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Microgels Composed of Poly(ethylene imine) and Carboxymethoxycoumarin: pH-Dependent and Photodependent Integrity

Hyun Ju Cha, Jing Dai, Jin-Chul Kim
College of Biomedical Science and Institute of Bioscience and Biotechnology, Kangwon National University, 192-1, Hyoja 2 Dong, Chunchon, Kangwon-Do 200-701, Korea
Correspondence to: J.-C. Kim (E-mail: jinkim@kangwon.ac.kr)

ABSTRACT: We developed novel microgels by taking advantage of electrostatic interactions between poly(ethylene imine) (PEI) and carboxymethoxycoumarin (CMC) and hydrophobic interactions among CMCs. CMC was obtained by the hydrolysis of 7-ethoxycarbonyl methoxycoumarin, which was derivatized from 7-hydroxycoumarin. The microgels were prepared by the mixture of PEI solutions (pH 5.0 and 7.5) with CMC solutions of the same pHs so that the molar ratio of PEI to CMC was 1:23. The size of the microgels prepared at pH 7.5 (a few nanometers) was much smaller than that of the microgels prepared at pH 5.0 (a few micrometers); this was possibly due to the more electrostatic interaction of the PEIs and CMCs at higher pH values. The microgels disintegrated when the pH of medium (e.g., pH 7.5) changed to strongly acidic (e.g., pH 3.0) and strongly alkaline (e.g., pH 9.0). Under acidic conditions, PEI hardly interacted with CMC because of the lack of ionization. Under alkaline conditions, the PEI was electrically neutralized, so no electrostatic repulsion developed, and this led to collapsed microgels. In addition, CMCs contained in the microgels were readily photodimerized as much as free CMCs. The microgels developed in this study could be used as drug vehicles that respond to pH changes and photoirradiation. © 2012 Wiley Periodicals, Inc. J. Appl. Polym. Sci. 129: 644–651, 2013

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INTRODUCTION

Coumarin(1-benzopyran-2-one) belongs to the benzopyrone class, and it is biosynthesized in many plants and can also be prepared by a Perkin reaction between salicyl aldehyde and acetic anhydride.[1,2] Because their photochemical properties, coumarin and its derivatives have been used as triggers in photoresponsive vehicles, which release their contents in a controlled manner in response to UV light irradiation.[3] The photodimerization of coumarins takes place under UV irradiation.[4,5] The double bonds of pyranones break, and as a result, cyclobutane bridges are formed between two molecules of the coumarins. Also, the dimmers are cleaved to monomers by the irradiation of a shorter UV wavelength (<260 nm).[6–8] Photoresponsive liposomes were prepared by the immobilization of hydrophobically modified water-soluble polymers containing coumarin moieties on their surfaces.[6] When the liposomes were subjected to a UV irradiation, the coumarin moieties were photodimerized, so the polymers took a contracted form, and this imposed a mechanical stress on the liposomal membranes. This may have caused packing defects in the membrane, and the contents entrapped in the liposomes were released through the packing defects. Photoresponsive polymeric micelles were prepared by the subjection of the dispersion of amphiphilic block copolymers having a hydrophilic block of poly(ethylene oxide) and a hydrophobic block of coumarin methacrylate in a polar solvent to UV irradiation.[5,9] A photoresponsive nanogel was prepared by the heating of an aqueous solution of a copolymer composed of hydrophilic blocks and thermosensitive blocks containing coumarins to a temperature above the lower critical solution temperature; the coumarin moieties were photodimerized, and the micelle solution was cooled to a temperature below lower critical solution temperature.[3]

In this study, we prepared novel microgels by taking advantage of electrostatic interactions between poly(ethylene imine) (PEI) and carboxymethoxycoumarin (CMC) and hydrophobic interactions among CMCs. The amino groups of PEI electrostatically interacted with the carboxyl groups of CMC, so the intermolecular/intramolecular electrostatic repulsion of PEIs decreased, and this led to the conformational change from a stretched form to a randomly coiled form. In addition, the CMCs attached to PEIs hydrophobically interacted with one another so the CMCs could act as a crosslinker for the PEIs. Because of the

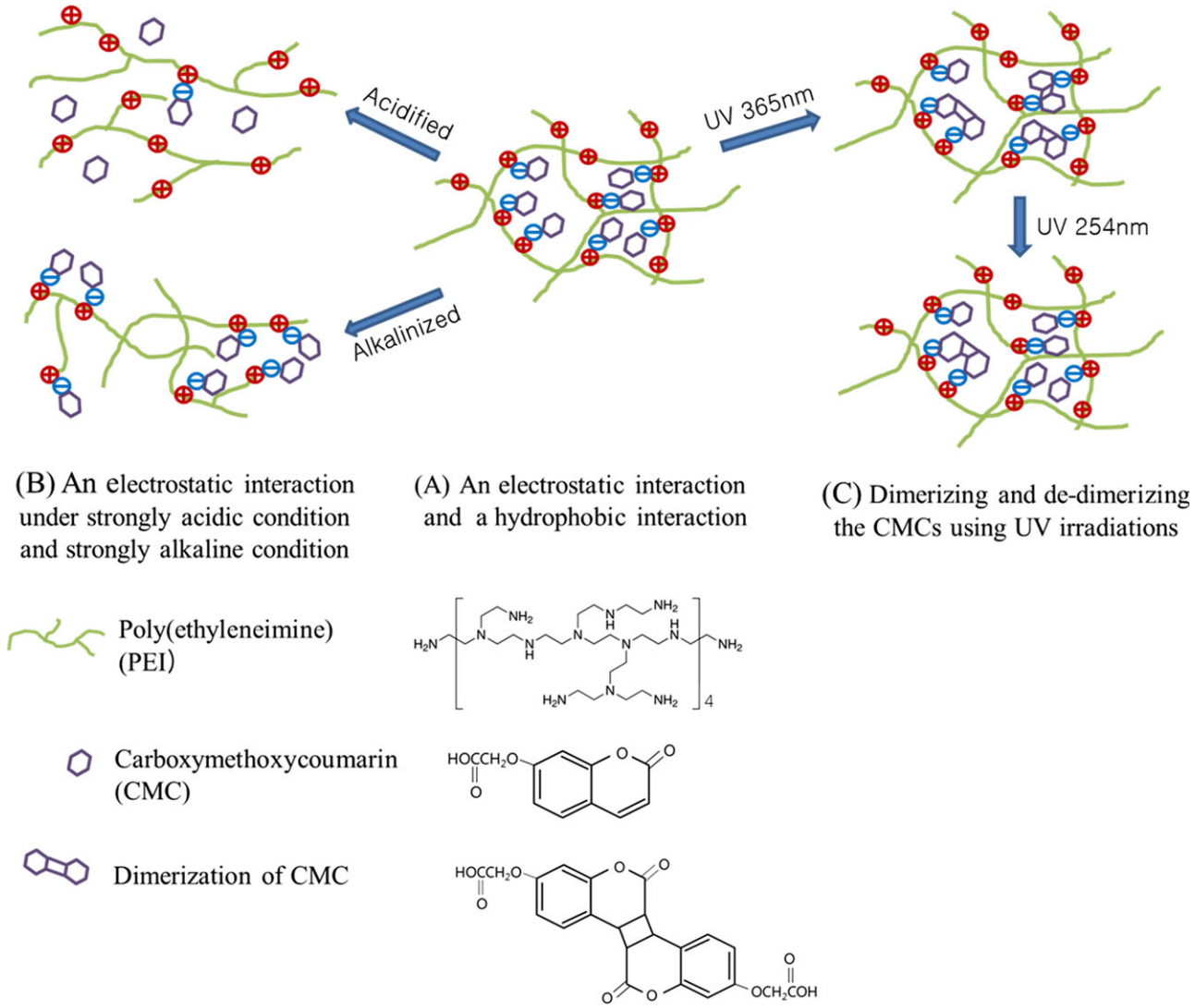


Figure 1. (A) Microgels are formed by electrostatic interactions between PEI and CMC and hydrophobic interactions among CMCs. (B) Because the electrostatic interaction between the carboxylic groups of CMC and the amino groups of PEI will be weak at a strong acidic condition and at a strong alkali condition, the microgels are likely to be disintegrated at those conditions. (C) The crosslinking density of the microgels can be controlled by the dimerization and dedimerization of the CMCs with UV irradiation. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

electrostatic interactions between PEI and CMC and the hydrophobic interactions among CMCs, microgels composed of PEI and CMC were formed. Because the electrostatic interaction between the carboxylic groups of CMC and the amino groups of PEI were weak under strongly acidic conditions and strongly alkaline conditions, the microgels were likely to be disintegrated under those conditions. Also, the crosslinking density of the microgels could be controlled by the dimerization and dedimerization of the CMCs with UV irradiation (Figure 1).

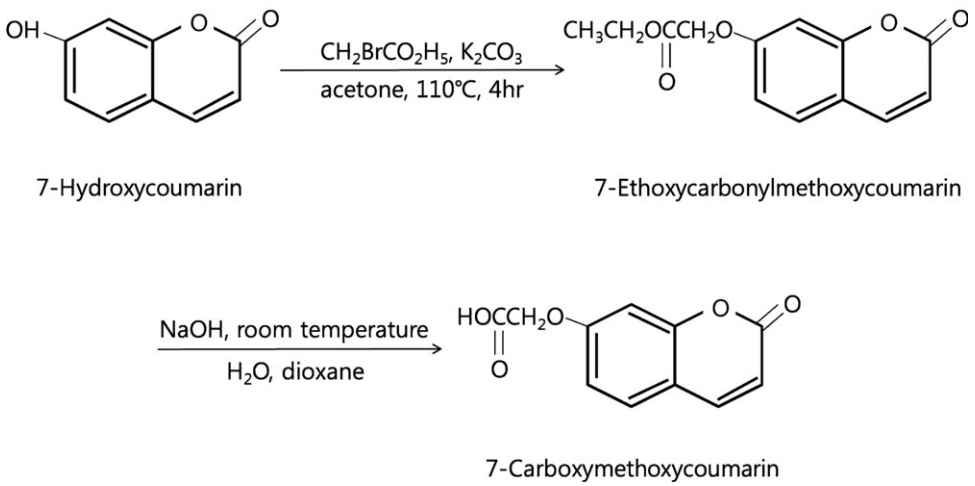
EXPERIMENTAL

Materials

7-Hydroxycoumarin [molecular weight (MW) = 162], ethyl bromoacetate, potassium carbonate, PEI (MW = 2000), and Trizma base (MW = 121.14) were purchased from Sigma-Aldrich Co. (St. Louis, MO). Glycine (MW = 75.37) was purchased from Bio Basic, Inc. (Ontario, Canada). 2-(*N*-Morpholino) ethane sulfonic acid (MES) monohydrate was purchased from BioShop, Inc. (Burlington, Canada). Water was doubly distilled in a Milli-Q water purification system (Millipore Corp., Billerica, MA, USA) until the resistivity was 18 MΩ/cm. All other reagents were analytical grade.

Synthesis of 7-CMC

7-Carboxymethoxcoumarin was derived from 7-hydroxylcoumarin by a method described in a previous report.[10] First, 7-ethoxycarbonyl methoxycoumarin was prepared by the refluxing of a mixture of 7-hydroxycoumarin (10.0 g, 61.7 mmol), ethyl bromoacetate (12.4 g, 74.3 mmol), and potassium carbonate (5.0 g, 36.0 mmol) in acetone (300 mL) at around 110°C for 4 h. The mixture was cooled down to room temperature, and



Scheme 1. Scheme for the preparation of the title compound.

acetone was evaporated under reduced pressure on a rotary evaporator (digital water bath SB-651, Eyela, Tokyo, Japan). The dry residue was dissolved in 500 mL of ethanol, and the salt (potassium carbonate) was removed by filtering through a filter paper (Whatmann no. 2, Maidstone, UK). 7-Ethoxycarbonyl methoxycoumarin was recrystallized from the filtrate and kept in an oven at 50°C. 7-CMC was obtained by the subjection of 7-ethoxycarbonyl methoxycoumarin to a hydrolysis. 7-Ethoxycarbonyl methoxycoumarin (14.0 g, 27.9 mmol) was dissolved in a mixed solution of sodium hydroxide (16.0 g, 200 mmol), 1,4-dioxane (280 mL), and water (400 mL), and the hydrolysis was done at room temperature for 24 h. To precipitate out the product (7-CMC), the reaction solution was acidified with hydrochloric acid in an ice bath. After the solution was filtered through a filter paper, the precipitated product (7-CMC) was air-dried overnight. The product was purified by recrystallization in ethanol. First, it was dissolved in 500 mL of ethanol contained in a 1-L beaker, and the solution was boiled until the volume decreased to less than 200 mL. The heated concentrated solution was cooled down to room temperature and left for 2 h to crystallize 7-CMC. The product was filtered with a filter paper, and the cake was dried in an oven that was kept at 50°C (Scheme 1).

^{1}H-NMR Spectra

7-Ethoxycarbonyl methoxycoumarin and 7-CMC were further dried with P_2O_5 in a desiccator of reduced pressure. They were dissolved in hexadeuterated dimethyl sulfoxide, respectively, and the spectra were taken with a Bruker Avance 400 spectrometer (Karlsruhe, Germany) in the Central Laboratory of Kangwon National University.

Solubility of 7-CMC

An excess amount of 7-carboxycoumarin was added to 10-mL aliquots of buffer solutions (pH 3.0-9.0) in 10-mL vials. The vials were put on a roller mixer operating at 40 rpm and left for 24 h. After the buffer solutions containing CMC were filtered through a syringe filter (pore size = 0.45 μm), the absorbance of the filtrate was measured at 323 nm on a UV spectrophotometer (6505 UV-visible spectrophotometer, Jenway, Staffordshire, UK). The calibration curve for each pH value was set up with the CMC solutions in each buffer solution, in which the CMC concentrations were 0.0031–0.1 mg/mL. Glycine buffer was used for pH 3.0 and 4.0, MES buffer was used for pH 5.0 and 6.0, and Trizma base buffer was used for pH 7.0–9.0.

Measurements of the ζ Potentials

The pH-dependent electrical charges of the PEI, CMC, and PEI/CMC mixture in aqueous solution were investigated by measurement of the ζ potentials on a ζ potential meter (ZetaPlus90, Brookhaven Instrument Co., Holtsville, NY, USA). The PEI solution (50% w/w) was diluted with buffer solutions (pH 7.5–10.5) so that the concentration was 4.98 mg/mL (2.48 m*M*). CMC was dissolved in the buffer solution, the concentration was 12.59 mL (57.2 mM). When the PEI/CMC mixture solutions were prepared, the PEI solution (50%, w/w) was diluted with CMC solutions (12.65 mg/mL, dissolved in buffer solutions at pH 7.5–10.5) so that the concentration of PEI was 4.98 mg/mL (2.48 m*M*) and 12.59 mg/mL (57.2 m*M*).

Preparation of the Microgels

Microgels were prepared by the dilution of 0.2 g of PEI solution (50%, w/w) with 20 mL of CMC solution (12.65 mg/mL, dissolved in buffer solutions at pH 5.0 and 7.5) so that the final concentration of PEI was 4.98 mg/mL (2.48 m*M*) and that of CMC was 12.59 mg/mL (57.2 mM). The PEI/CMC solutions were freeze-dried for the observation of microgels by scanning electron microscopy (SEM (Hitachi, Ltd., Tokyo, Japan), in the Central Lab- oratory Center of Kangwon National University, Chuncheon, Korea).

pH-Dependent Integrity of the Microgels

Microgel suspensions (1 mL, pH 7.5) were diluted with 9 mL of glycine buffer solution (pH 3.0) and 9 mL of Trizma base buffer solution (pH 9.0). The pHs of the diluted suspensions were adjusted to 3.0 and 9.0 with 1*N* HCl and 1*N* NaOH. The shape of the freeze-dried residues was observed with SEM.

Photosensitivity of the CMC Bound to the PEI Microgels

The photodimerizations of the CMC bound to the PEI microgel and free CMC were investigated under cyclic UV irradiation. CMC was dissolved in a buffer solution (pH 7.5) so that the concentration was 12.59 mg/mL (57.2 m*M*). The PEI/CMC

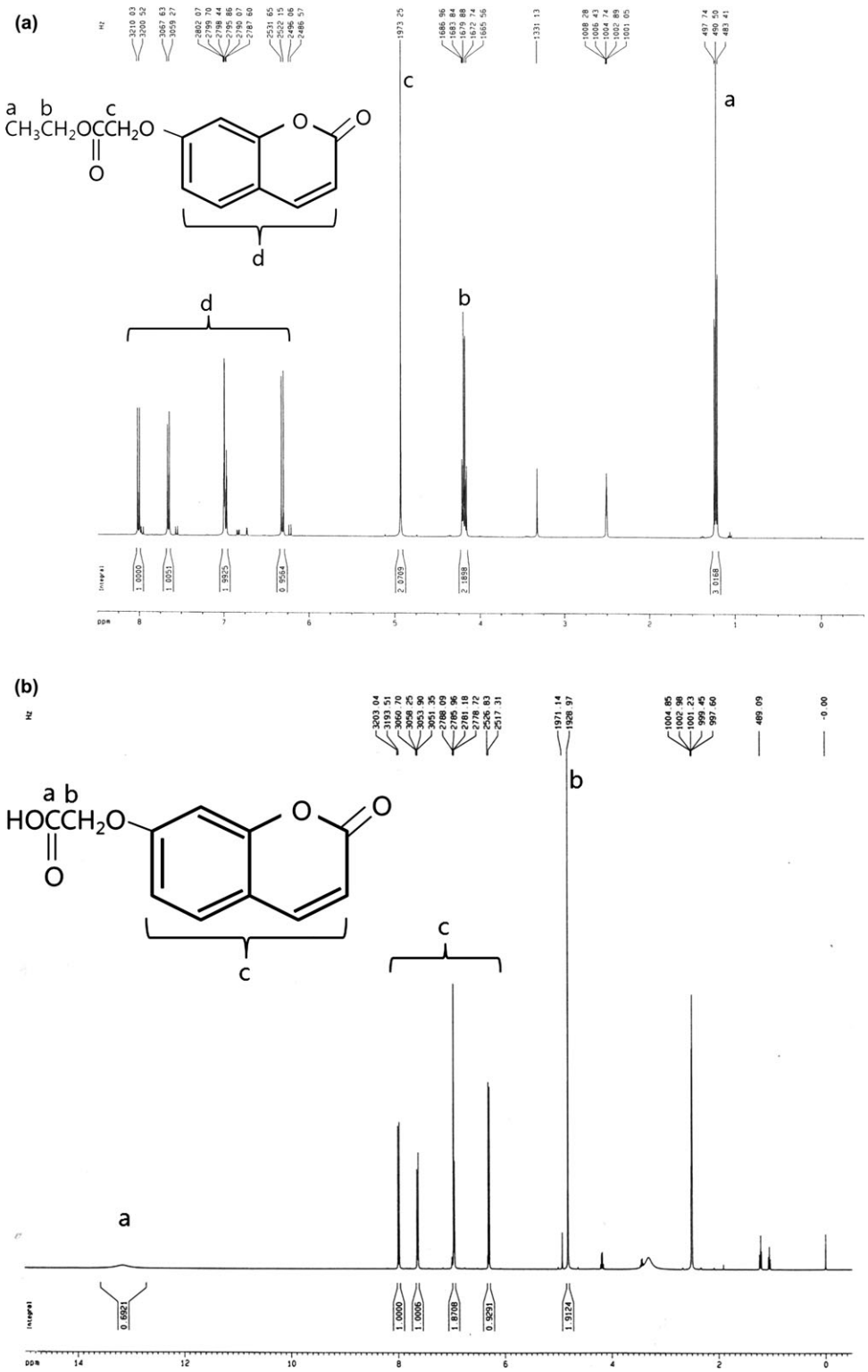


Figure 2. [1]H-NMR spectra of (A) 7-ethoxycarbonyl methoxycoumarin and (B) 7-CMC.

microgels prepared by the dilution of PEI solution (50% w/w) with CMC solutions (12.65 mg/mL) were dissolved in a buffer solution (pH 7.5) so that the concentration of PEI was 4.98 mg/mL (2.48 m*M*) and that of CMC was 12.59 mg/mL (57.2 m*M*). The CMC solution and the PEI/CMC microgel suspension were subjected to cyclic UV irradiation [365 nm (400 W) for 20 min and then 254 nm (6 W) for 10 min]. The dimerization degree was determined as follows:[11]

$$\text{Dimerization } (\%) = (1 - A_t/A_0) \times 100\% \quad (1)$$

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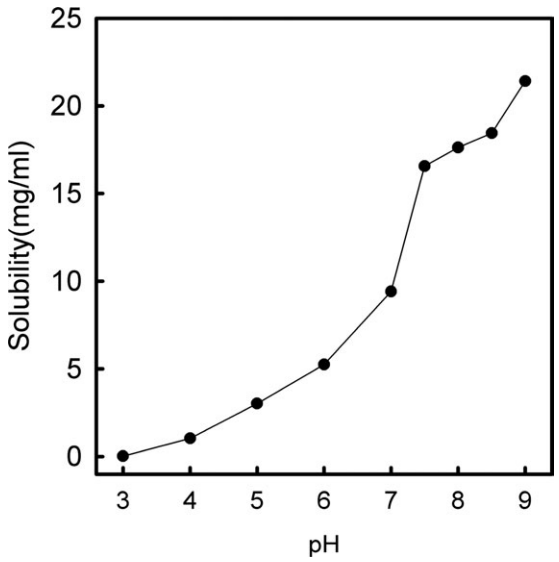

Figure 3. Solubility of CMC in buffer solutions. Glycine buffer was used for pH 3.0 and 4.0, MES buffer was used for pH 5.0 and 6.0, and Trizma base buffer was used for pH 7.0–9.0.

where A_0 is the absorbance at 323 nm before irradiation with UV light and A_t is the absorbance after irradiation with UV light.

RESULTS AND DISCUSSION

^{1}H-NMR Spectra

Figure 2 shows the ^{1}H-NMR spectra of 7-ethoxycarbonyl methoxycoumarin and 7-CMC (400 MHz, hexadeuterated dimethyl sulfoxide, δ). In the ^{1}H-NMR spectrum of 7-ethoxycarbonyl methoxycoumarin [Figure 2(A)], the signals at 7.65–7.70 originated from the CH of the pyranone ring, the signals at 7.35–7.40 and 6.85–6.90 ppm were ascribed to the CH of benzene rings, the signals at 6.25–6.30 ppm were due to the CH of the pyranone ring, the signals at 4.93 ppm were from the CH_2 of the methoxy group, the signals at 4.22–4.30 ppm were from the CH_2 of ethoxy group, and the signals at 1.28–1.32 ppm originated from the CH_3 of the ethoxy group. In the ^{1}H-NMR spectrum of 7-CMC [Figure 2(B)], the signal at 13.15 ppm was ascribed to the carboxyl group, the signals at 7.98–8.04 ppm originated from the CH of the pyranone ring, the signals at 7.60–7.65 and 6.93–6.98 ppm were ascribed to the CH of benzene rings, the signals at 6.28–6.33 ppm were due to the CH of the pyranone ring, and the signals at 4.82–4.93 ppm were due to the CH_2 of the methoxy group. These signal assignments were in good agreement with results reported in a previous work.[12]

Solubility of 7-CMC

Figure 3 shows the solubility of CMC in the buffer solutions (pH 3.0–9.0). CMC was sparingly soluble under strongly acidic conditions (e.g., pH 3.0), but it was readily soluble under neutral and alkaline conditions. The solubilities of CMC at pHs of 3.0, 4.0, 5.0, 6.0, 7.0, 7.5, 8.0, 8.5, and 9.0 were 0.02, 1.05, 3.02, 5.25, 9.42, 16.56, 17.62, 18.44, and 21.42 mg/mL, respectively. The solubility of an ionizable compound in an aqueous phase is proportional to the ionization degree,[13,14] and according to an equation derived from Henderson Hasselbalch's equation, the ionization degree of an acidic compound increases with the pH value {Ionization degree $= 1/[1 + 10^{(pK_a - pH)}] \times 100$}. This may account for why the solubility of CMC increased with the pH of the medium, as shown in Figure 3.

Measurements of ζ Potentials

Figure 4 shows the ζ potentials of PEI, CMC, and PEI/CMC in buffer solutions (pH 7.5–10.5). The ζ potential of PEI decreased with increasing pH of the medium. For example, the value decreased from + 27 to 10 mV when the pH increased from 7.5 to 10.5. This was because the amine groups were deprotonated with increasing pH. The ζ potential of CMC also decreased with increasing pH of the medium. For example, the value decreased from −2 to −24 mV when the pH increased from 7.5 to 10.5. This was because the carboxyl group was ionized with increasing pH. The ζ potential of PEI/CMC also decreased with increasing pH of the medium, and the values fell between the ζ potentials of the PEI and those of CMC, except the value at pH 7.5. This was because the positively charged PEI electrostatically interacted with the negatively charged CMC. The point of zero charge was observed around pH 9.0. The molar ratio of PEI to CMC in the PEI/CMC solution was 1:23. The ionization degree of an acidic compound is expressed as follows: $1/(1 + 10^{(pK_a - pH)}) \times 100$, so the ionization degree of the carboxylic group of CMC at pH 9.0 was almost 100%. The number of amino groups per one molecule of PEI was 46 on average, and the ionization degree of the amino group was 50% at pH 9.0 because the pK value of the amino group of PEI was around the pH value. Accordingly, the number of negative charge points was the same as that of positive charge points at pH 9.0 when the molar ratio of PEI to CMC in the PEI/CMC solution was 1:23. This may account for why the point of zero charge was observed at around pH 9.0.

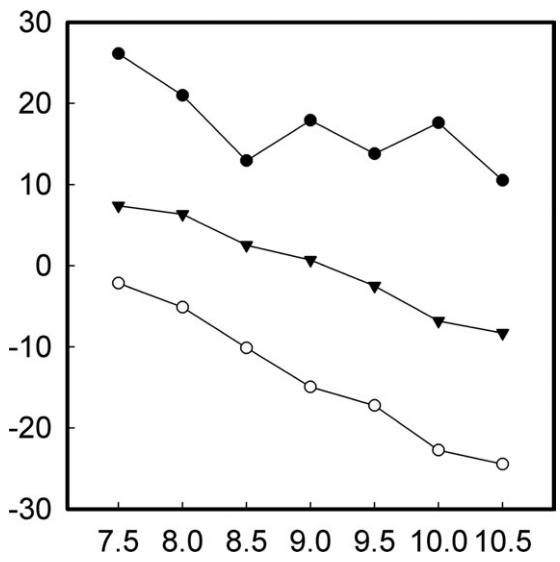

Figure 4. ζ potentials of (●) PEI, (○) CMC, and (▼) PEI/CMC in buffer solutions (pH 7.5–10.5).

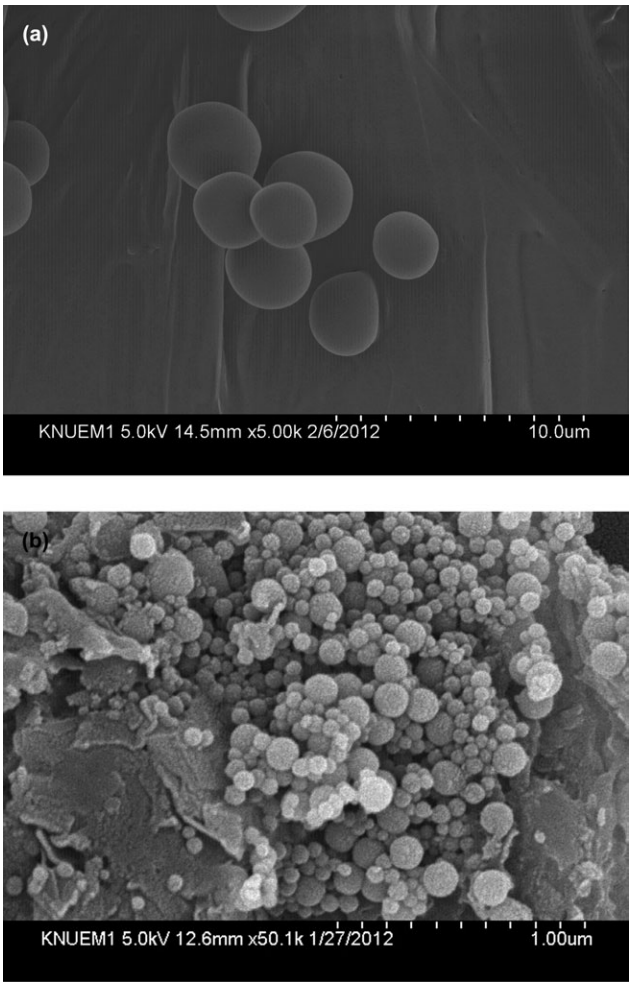

Figure 5. SEM photos of microgels prepared in (A) MES buffer (pH 5.0) and (B) Trizma base buffer (pH 7.5). The bar in photo part A represents 10 μm, and the bar in part B represents 1 μm.

SEM of the Microgels

Figure 5 shows the SEM results of the microgels prepared in buffer solutions of pH 5.0 and 7.5. In the buffer solution of pH 5.0, fused microgels were observed, and the sizes were less than 10 μm. At pH 5.0, the ionization degree of the PEI's amines was calculated to be 100% by an equation derived from Henderson Hasselbalch's equation for a basic compound: $\{1 + [10^{(pK_b - pH)}]^{-1}\}^{-1} \times 100$, and the ionization degree of the CMC's carboxyl group was calculated to be 61.3% by an equation derived from Henderson Hasselbalch's equation for an acidic compound: $1/[1 + 10^{(pK_a\text{-}pH)}] \times 100$. Therefore, the ratio of ionized amino groups to ionized carboxyl groups was calculated to be about 46 $\times$ 1.0:23 $\times$ 0.613 = 1:0.31. This means that 31% of the amino groups of PEI could electrostatically interact with all of the charged CMCs (61.3% of the CMCs) if we assumed that all of the charged functional groups participated in the electrostatic interaction. Because of the neutralization of the amino groups of PEI, the intermolecular/intramolecular repulsions decreased, and this led to the conformation change of the molecule from a stretched form to a randomly coiled form. In addition, the CMCs electrostatically attached to the PEIs acted as a crosslinker for PEI because the benzene rings could hydrophobically interact with one another. The electrical neutralization of PEIs and the hydrophobic interaction of the attached CMCs are believed to be main reasons for the formation of microgels. On the other hand, much smaller particles were formed in the buffer solution of pH 7.5 [Figure 5(B)]. At pH 7.5, the ratio of ionized amino groups to ionized carboxyl groups was calculated to be about 46 $\times$ 0.997:23 $\times$ 0.998 = 2:1. This means that 50% of the ionized amino groups of PEI (49.85% of the amino groups of PEI) could electrostatically interact with all of the ionized CMCs (99.9% of the CMCs) with the assumption that all of the charged functional groups participated in the electrostatic interaction. Intermolecular/intramolecular repulsive forces were developed within the microgels because of the ionized amino groups, which were not associated with the ionized CMCs. Because the number of unassociated amino groups was theoretically less at pH 7.5 than at pH 5.0, smaller microgels were formed at higher pH values.

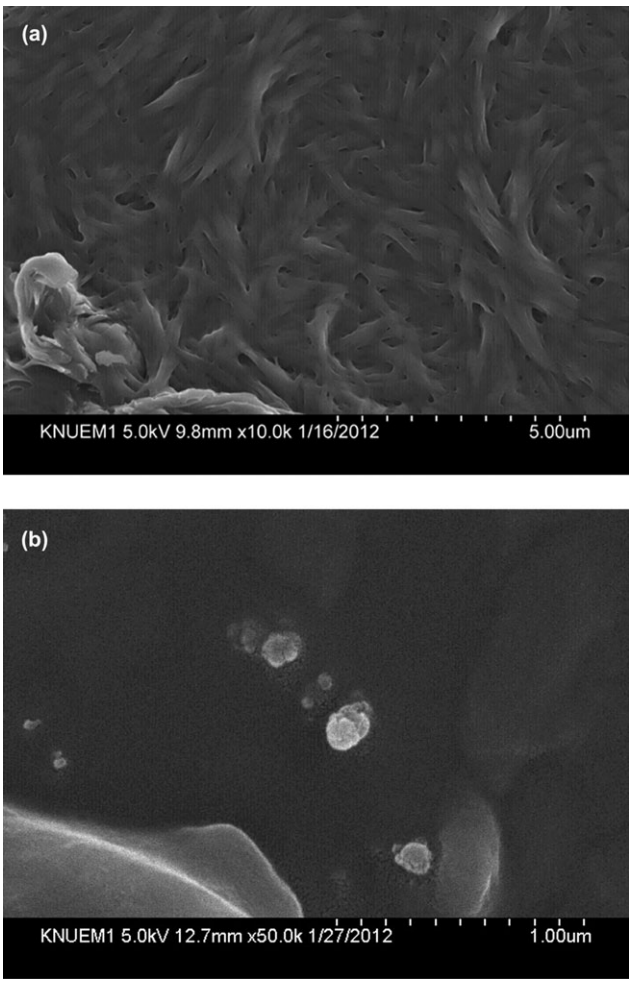

Figure 6. SEM photos after the microgel suspensions (pH 7.5) were (A) acidified to pH 3.0 and (B) alkalinized to pH 9.0. The bar in part A represents 5 μm, and the bar in part B represents 2 μm.

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pH-Dependent Integrity of the Microgels

Figure 6 shows SEM photos after the microgel suspensions (pH 7.5) were acidified to pH 3.0 and alkalinized to pH 9.0. After being acidified, the microgels could hardly be found, as shown in Figure 6(A). At pH 3.0, the ionization degree of the PEI's amines was calculated to be 99.99%, and the ionization degree of the CMC's carboxyl groups was calculated to be 1.56% Therefore, the ratio of ionized amino groups to ionized carboxyl groups was calculated to be about $46 \times 0.9999{:}23 \times 0.0156 = 1{:}0.0078$. This indicated that only 0.78% of the ionized amino groups could be neutralized by the ionized CMCs, and most of the ionized amines were unassociated. Accordingly, with the change in the pH of medium from 7.5 to 3.0, the PEI molecules underwent a conformational change from a randomly coiled form to a stretched form, and this led to the disintegration of the microgels. In addition, the number of CMC molecules electrostatically attached to one molecule of PEI was calculated to decrease from 22.95 to 0.36 upon acidification, so an intermolecular/intramolecular hydrophobic interaction, which could take place because of the CMCs attached to PEIs, decreased to disintegrate the microgels. On the other hand, after the microgel suspensions (pH 7.5) were alkalinized to pH 9.0, particles of less than 100 nm were observed together with nonspherical lumps of a few micrometers [Figure 6(B)]. At pH 9.0, the ionization degree of PEI's amines was calculated to be 50%, and the ionization degree of CMC's carboxyl groups was calculated to be 99.9% Therefore, the ratio of ionized amino groups to ionized carboxyl groups was calculated to be about $46 \times 0.5{:}23 \times 0.999 = 23{:}22.89 = 1{:}1$. This indicated that all of the ionized amino groups could interact with all of the ionized CMCs. As a result, the net charge was zero, and no repulsive forces were likely to develop. In fact, the ζ potential of PEI/CMC was around zero at pH 9.0 (Figure 4). This may account for the microgels collapsing to smaller and irregularly shaped particles upon alkalization.

Photosensitivity of the CMC Bound to the PEI Microgels

Figure 7 shows the dimerization degree of the CMC bound to the PEI microgel and free CMC under cyclic UV irradiation. The dimerization degree of the free CMC increased to 43% in the 20 min of irradiation at 365 nm, and it decreased to 37% in the 10 min of irradiation at 254 nm. The coumarin and its derivative are known to be dimerized under UV irradiation ($\lambda = 365$ nm) because the double bonds of the pyranones break to form cyclobutane bridges due to photo energy. The dimmers are converted to monomers under the irradiation of a shorter wavelength UV light (e.g., $\lambda = 254$ nm) because of the photocleavage of the cyclobutane bridges.[8,11,15] As in the first cycle, subsequent cyclic irradiations gave a rise to cyclic dimerizations/dedimerizations. In each cycle, the dedimerization degree was less than the dimerization degree; this occurred possibly because the UV irradiation of $\lambda = 254$ nm allowed for not only dedimerization but also dimerization.[3] As the number of cycles increased, the degree of dimerization increased in a saturation manner. This occurred possibly because equilibrium between the dimerization and dedimerization was reached in a prolonged UV irradiation.[15] The profile of the dimerization degree of CMC bound to the PEI microgel was almost the same as that of free CMC. That is, the PEI microgels had little effect on the dimerization degree of CMC. At pH 7.5, the ionization degree of PEI's amines was calculated to be 99.7%, and the ionization degree of CMC's carboxyl groups was calculated to be 99.8%. The molar ratio of amine to carboxyl groups in the CMC/PEI microgel was calculated to be 2:1 (the molar ratio of PEI to CMC was 1:23, and the number of amino groups per one molecule of PEI was 46). Therefore, the ratio of ionized amino groups to ionized carboxyl groups was calculated to be about $46 \times 0.997{:}23 \times 0.998 = 2{:}1$. This means that all of the CMCs could electrostatically interact with the PEIs. Nevertheless, the dimerization degree of the CMCs was affected little by the PEI microgel. This occurred possibly because the double bond, which was involved in the photodimerization, belonged to the pyranone ring, and the carboxylic group, which was related to the electrostatic interaction, belonged to the benzene ring. Therefore, we can say that CMC maintained its photosensitivity, even in the PEI microgels.

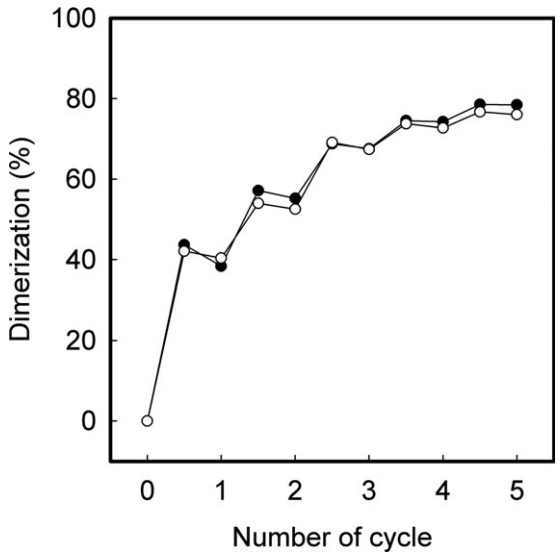

Figure 7. Dimerization degree of (○) CMC bound to the PEI microgel and (●) free CMC under cyclic UV irradiation.

CONCLUSIONS

Novel pH-responsive and photoresponsive microgels were developed with electrostatic interactions between PEI and CMC and hydrophobic interactions among CMCs. The microgels were formed when PEI solutions (pH 5.0 and 7.5) were mixed with CMC solutions of the same pHs at a molar ratio of PEI to CMC of 1:23. The size of microgels in a buffer solution (pH 7.5), a few nanometers, was much smaller than that of microgels in a buffer solution (pH 5.0), a few micrometers. The electrostatic repulsions developed within the microgels were believed to be a major factor affecting the size. The microgels disintegrated when they were exposed to strongly acidic conditions (e.g., pH 3.0) and strongly alkaline conditions (e.g., pH 9.0). No significant electrostatic interactions between the PEIs and CMCs could take place under strongly acidic conditions because of the lack of negative charge points. PEI could be electrically neutralized by CMC under alkaline conditions, so no repulsive force was developed within the microgels; this led to the collapse of the microgels. In addition, the CMCs contained in the microgels were readily photodimerized and dedimerized under UV irradiation, so the crosslinking density

of the microgel could be photonically controlled. Even though coumarin is moderately toxic to the liver and kidneys and would be largely metabolized to 7-hydroxycoumarin in humans, some researchers have stated that a low level of coumarin from the diet and fragrances used in cosmetics would not produce any hepatotoxicity, even with a lack of 7-hydroxylase activity.[16] There have been many studies about drug carriers containing coumarins, such as hydrogels, nanogels, and micelles.[17–19] The reversible photodimerization properties of coumarin have been used in the development of photoresponsive drug-delivery systems, so the microgels developed in this study could be used in photoresponsive drug-delivery system as well. Several kinds of water-soluble anticancer drugs, such as doxorubicin hydrochloride and topotecan, have been loaded into hydrogels, microgels, and nanogels.[20,21] It was also reported that dipyridamole, an antithrombogenic agent, has been loaded in a photoresponsive nanogel.[18] A water-soluble anticancer drug is believed to be one of candidates that could be loaded into the microgels developed in this work. The photoresponsive microgels could be modified with a ligand and applied on the diseased tissue during an operation. The drug contained in the microgel could be released under UV irradiation to reduce side effects through the focus of the UV irradiation on the target tissues or cells.

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