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Alginate microspheres incorporating poly(hydroxyethyl acrylate-co-coumaryl acrylate-co-2-ethylhexyl acrylate) : Effect of temperature and UV irradiation on FITC-dextran release

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Abstract−Alginate microspheres incorporating poly(hydroxyethyl acrylate-co-coumaryl acrylate-co-2-ethylhexyl acrylate) (P(HEA-CA-EHA)) were prepared using the water droplets of W/O emulsion as a template. P(HEA-CA-EHA) was prepared by a free radical reaction and the HEA/CA/EHA molar ratio was calculated to be 96.1 : 2.0 : 1.9 on the ^{1}H NMR spectrum. The copolymer exhibited a lower critical solution temperature around 27 ºC in distilled water. The microspheres were prepared by using O/W emulsion as a template and Ca^{2+} as a cross-linker for alginate. The resulting microspheres were subjected to UV (365 nm) irradiation for the cross-linkage of P(HEA-CA-EHA). The irradiation of UV (254 nm) to the UV (365 nm)-treated microsphere promoted the release of FITC-dextran (MW. 4,000), possibly due to the cleavage of the CA residue dimers. However, the temperature change had little effect on the release degree in the range of 21 ºC to 37 ºC.

Keywords: Alginate, P(HEA-CA-EHA), Emulsion, Microsphere, Release

INTRODUCTION

Alginate, an anionic polysaccharide, has been frequently used in the preparation of drug carrier due to its abundance in nature, biocompatibility, gel-forming property with multivalent cations (e.g. Ca^{2+}, Mg^{2+} and Al^{3+}), and ease of the chemical functionalization [1]. Stimuli-responsive alginate microspheres were prepared by using a functionalized alginate as a major component or including it in the microsphere matrix. Poly (*N*-isopropylacrylamide) (PNIPAM), a thermo-responsive polymer, was grafted to alginate, and the beads of alginate/PNIPAM graft were prepared using Ca^{2+} as a cross-linker [2]. They released their content in a controlled manner in response to the temperature change of release medium. PNIPAM was thought to act as a thermal valve in the alginate matrix because it thermally contracts and expands. For the same purpose, the surface of alginate beads was decorated with the copolymers of *N*-isopropylacrylamide and dimethylaminoethyl methacrylate (P(NIPAM-co-DMAEMA)s) by taking advantage of an intermolecular electrostatic interaction [3]. On the other hand, the copolymer of NIPAM, methacrylic acid, and octadecyl acrylate (P(NIPAM-*co*-MAA-*co*-ODA) were physically included in alginate beads to obtain a pH-responsive carrier [4]. The copolymer was thought to act as a pH valve in the alginate matrix because the ionization degree of MAA strongly depends on the pH value of medium, and the copolymer would change its configuration in response to the pH change. Alginate beads were decorated with polylysine through an intermolecular electrostatic interaction, and they showed a pH-responsive release [5]. The electrostatic interaction between the surface of alginate bead and polylysine would be stronger at an acidic pH value, suppressing the release from the beads. Interpenetrating network (IPN) beads were prepared by dropping the aqueous mixture solution of alginate and poly(vinyl alcohol)-coumarin conjugate into Ca^{2+} solution and by photo cross-linking the coumarin residues [6]. The beads exhibited a photo-responsive release because the cross-linking density could be controlled by the UV-induced photo-reaction of the coumarin residues.

In this study, poly(hydroxyethyl acrylate-co-coumaryl acrylate-co-2-ethylhexyl acrylate) (P(HEA-CA-EHA)) was included in the matrix of alginate microspheres for the preparation of a temperature- and photo-responsive carrier. P(HEA-CA-EHA)s were reported to thermally contract in an aqueous solution and have their own lower critical solution temperature depending on the composition. They can also change their configuration in response to a UV irradiation because the CA residues are photo-dimerized and de-dimerized under the irradiation of a UV light. Therefore, alginate microspheres including P(HEA-CA-EHA)s are believed to show a temperature- and a photo-responsive release (Fig. 1). P(HEA-CA-EHA)s were prepared by a free radical reaction and characterized in terms of the temperature-sensitivity and the photo-sensitivity. The microsphere was prepared by emulsifying the mixture aqueous solution of alginate and P(HEA-CA-EHA)s in mineral oil and solidifying the droplets using Ca^{2+}. The release degree of FITC-dextran from the microsphere was investigated by changing the temperature of the release medium. The effect of UV irradiation on the release was also investigated.

EXPERIMENTAL

1. Materials

Acryloyl chloride was purchased from TCI (Tokyo, Japan). Sodium alginate, mineral oil, sorbitan monooleate, fluorescein isothio-

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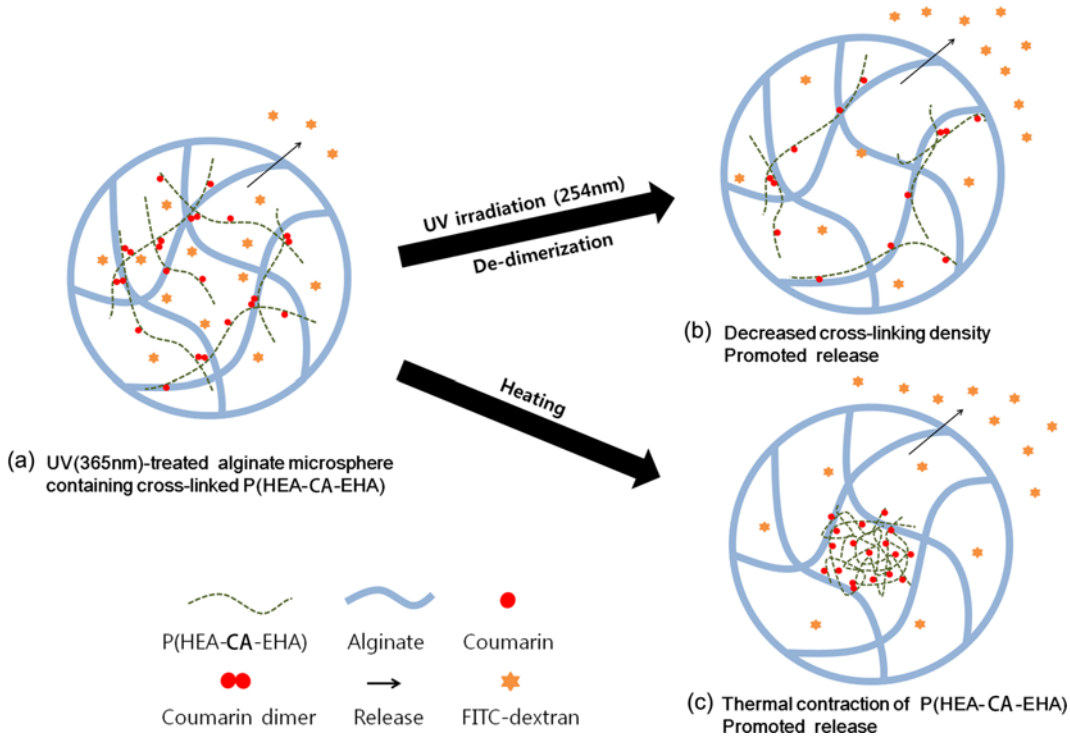

Fig. 1. Schematic representation of temperature- and UV-responsive alginate microsphere. Upon the UV irradiation (254 nm), the CA dimers of cross-linked P(HEA-CA-EHA)s in alginate microsphere will be de-dimerized and the cross-linking density will decrease, leading to promoted release ((a)→(b)). Upon heating, P(HEA-CA-EHA)s in alginate microsphere will thermally contract and the bead pores will be widened, resulting in promoted release ((a)→(c)).

cyanate-dextran (FITC-dextran, MW. 40,000), hydroxyethyl acrylate (HEA), 7-hydroxy coumarin, 2-ethylhexyl acrylate (EHA), and dimethylforamide (DMF) were purchased from Sigma Chemical co. (St. Louis, MO). a-a′-Azobis(isobutyronitrile) (AIBN) was provided by Junsei Chemical Co. (Japan). Calcium chloride was provided by Dae Jung Co. (Seoul, South Korea). N-(2-hydroxyethyl) piperazine-n′-(2-ethanesulfonic acid) (HEPES) was obtained from USB corporation (Cleveland, OH, USA). Water was doubly distilled in aMilli-Q water purification system (Millipore Corp, MA, USA) until the resistivity was 18 MΩ/cm. All other reagents were in analytical grade.

2. Preparation of P(HEA-CA-EHA)

P(HEA-CA-EHA) was prepared by a method described in a previous report [7]. HEA (2.230 g), CA (0.086 g) and EHA (0.074 g) were put in a 250 ml 3-neck round bottom flask so that the molar ratio was 96 : 2 : 2. DMF (20 ml) was put in the flask and the monomers were dissolved by stirring the mixture on a magnetic stirrer. AIBN (20 mg) was then added to the mixture solution as an initiator. After being degassed using nitrogen gas stream for 30 min, the mixture was subjected to free radical reaction by being heated to 75 °C and kept at the same temperature with reflux for 12 h. The reaction mixture was kept to stand at a room temperature until cooled, and it was poured into diethylether (300 ml) for the precipitation of the product (P(HEA-CA-EHA)). The precipitate was separated by filtration and it was re-precipitated in the non-solvent. The purified product was dried in an oven for further use.

3. ^{1}H NMR Spectroscopy

P(HEA-CA-EHA) was dried in a vacuum desiccator with P_2O_5 and then it was dissolved in DMSO-d6. The ^{1}H NMR spectrum of the copolymer was taken on a Bruker DPX 600 MHz spectrometer (Karlsruhe, Germany, in the Central Laboratory Center of Kangwon National University).

4. Observation of Phase Transition of P(HEA-CA-EHA) in Aqueous Phase

Phase transition of P(HEA-CA-EHA) in an aqueous solution was observed by a method described in a previous report [8]. P(HEA-CA-EHA) was dissolved in distilled water so that the concentration was 2% (w/v). In parallel, P(HEA-CA-HEA) and alginate were co-dissolved in distilled water so that each concentration was 2% (w/v). The temperature-dependent cloudiness of the polymer solutions was observed by determining the absorbance at 600 nm on a UV spectrophotometer (JENWAY 6505) equipped with a temperature controller (Mettler, JENWAY Peltier Controller) in the temperature range of 20 °C to 50 °C. The absorbance was recorded every 1 °C in the heating process.

5. Determination of CA Residues Dimerization of P(HEA-CA-EHA)

An aqueous solution of P(HEA-CA-EHA) was prepared by dissolving 0.01 g of the copolymer in 5 ml of distilled water. In parallel, the mixture solution of P(HEA-CA-EHA) and alginate was prepared by dissolving 0.1 g of alginate and 0.01 g of the copolymer in 5 ml of distilled water. The solutions were subjected to UV irradiation of 365 nm for 90 min and then 264 nm for the same period. The UV-treated polymer solutions were 10-folds diluted with distilled water for the determination of the dimerization degree of the CA residue. The dimerization degree was calculated by an equa-

tion presented in a previous report [9].

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

where, A_o is the absorbance of the polymer solutions at 327 nm before exposed to a UV irradiation, and A_t is the absorbance after exposed to a UV irradiation.

6. Preparation of Alginate Microspheres

Alginate microspheres incorporating P(HEA-CA-EHA) were prepared using the water droplets of W/O emulsion as a template [10]. 200 ml of mineral oil was put in a 500 ml beaker and then 4 ml of span 80, an emulsifier, was mixed with the oil. 50 ml of alginate solution (2%) or alginate/P(HEA-CA-EHA) mixture solution (1.5%/0.5%) in distilled water was put in the oil phase, and then the two phase system was homogenized in a homogenizer (Scientific Industries, Inc. G-560) for 10 min. While the W/O emulsion was being stirred with a magnetic bar, 17 ml of $CaCl_2$ solution (5%) in distilled water was added to the emulsion over 20 min to crosslink alginate in the water droplets, and it continued to be stirred for 4 hr. The microspheres were washed three times with 300 ml of acetone to remove oil and they were freeze-dried for further use.

7. Characterization of Microspheres

The content of P(HEA-CA-EHA) in the alginate/P(HEA-CA-EHA) microsphere were determined by colorimetrically analyzing the amount of CA residue. 10 mg of dry alginate/P(HEA-CA-EHA) microsphere was put in 10 ml of PBS (10 mM) contained in a 30 ml vial and it was stirred until the microspheres completely disintegrated. The absorbance of the solution was measured at 320 nm on a UV spectrophotometer, and the amount of CA residue was determined on an CA standard curve, which had been established by measuring the absorbance at 320 nm of CA solutions (2 mg/ml, in distilled water). Alginate microsphere and alginate/P(HEA-CA-EHA) microsphere were put on metal stubs, and they were coated with gold and observed in a scanning electron microscope (Jeol JSM-840A).

8. Effect of UV Irradiation on Release from Microsphere

Dry alginate microsphere and dry alginate/P(HEA-CA-EHA) microsphere were subjected to the irradiation of UV (365 nm, 400 W) for 10 hr. Each of the photo-treated microspheres, 0.3 g, was soaked in 2 ml of FITC-dextran solution (0.1% w/v, in distilled water) contained in a 10 ml vial, and it was kept to stand for three days at a room temperature under a dark condition. The microspheres were separated from the dye solution by filtrating the mixture through a filter paper (Whatman No. 541) and washed with distilled water. The dye-loaded microspheres were freeze-dried for the release experiment and for further UV-treatment. The microspheres, 0.02 g, were put in 5 ml of PBS (10 mM, pH 7.4) contained in a 20 ml vial and the mixtures were swirled on a roller mixer until they completely disintegrated. For the determination of the amount of dye loaded in the microspheres, the fluorescence intensities of the solutions obtained after the disintegration were measured at 480 nm with the excitation wavelength of 520 nm on a fluorescence spectrophotometer (Hitachi F2500, Japan). To investigate the effect of UV irradiation (254 nm) on the dye release, the UV (365 nm)-treated microspheres containing dye were additionally subjected to the irradiation of UV (254 nm, 6 W) for 10 hr. To observe the release property of the microspheres, 0.05 g of each of UV-untreated microspheres and UV-treated microspheres was put in 5 ml of HEPES buffer (30 mM, pH 7.0) contained in a 20 ml vial and it was whirled on a roller mixer for two days. The release medium, 0.1 ml, was taken at a given time,

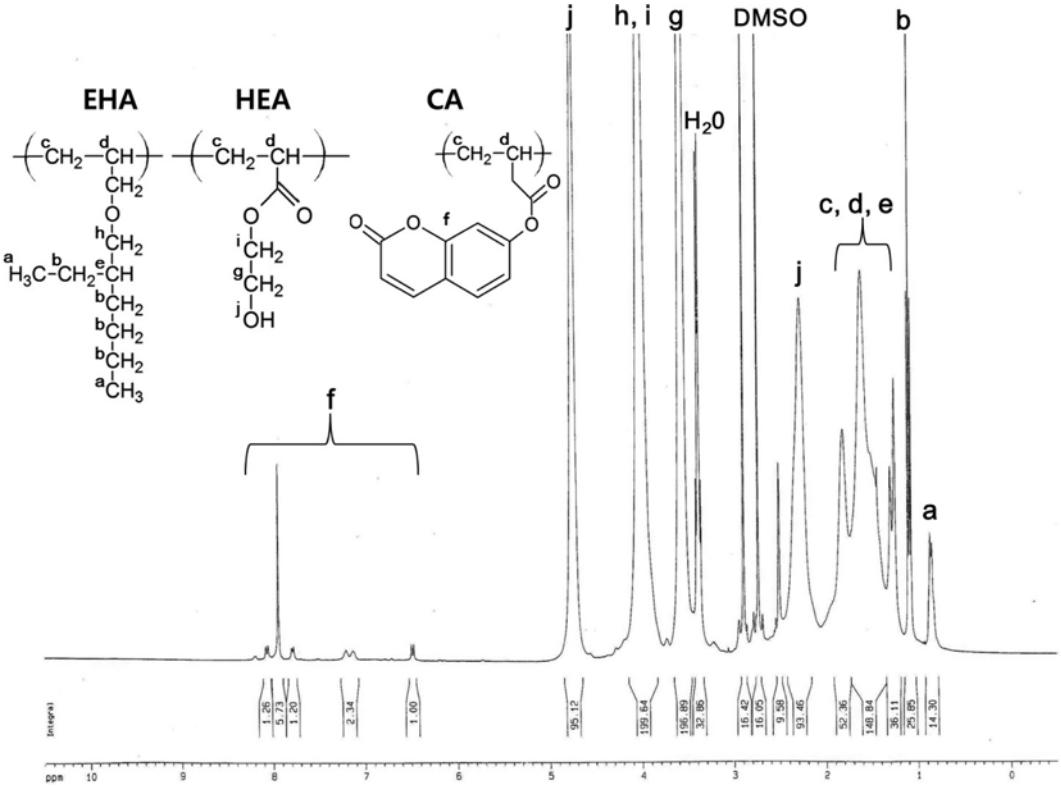

Fig. 2. ^{1}H NMR spectrum of P(HEA-CA-EHA).

and the fluorescence intensity was measured. The release degrees were defined as the percent of the amount of dye released with respect to the amount of dye loaded.

9. Effect of Temperature on Release from Microsphere

UV (365 nm)-treated and dye-loaded alginate microspheres, and UV (365 nm)-treated and dye-loaded alginate/P(HEA-CA-EHA) ones, 0.05 g of each, were put in 5 ml of HEPES buffer (30 mM, pH 7.0) contained in a 20 ml vial and it was whirled on a roller mixer for two days at the temperature of 21 ℃, 27 ℃, 30 ℃, and 37 ℃. The release degrees were determined as described previously.

RESULTS AND DISCUSSION

1. ^{1}H NMR Spectroscopy

Fig. 2 shows the ^{1}H NMR spectrum of P(HEA-CA-EHA). The vinyl protons were found at 1.6 ppm and 1.9 ppm. The methylene protons next to the ester bond of HEA were found at 4 ppm, the methylene protons next to the hydroxyl group of HEA were found at 4.7 ppm, and the ethyl group of HEA was found at 3.5 ppm. The coumaryl protons were found in the range of 6.5 ppm to 8.2 ppm. The methyl protons of EHA were found at 0.8 ppm, the methylene protons adjacent to the methyl group of EHA were found at 1.3 ppm, and the methylene protons next to the ester bond of EHA were found at 4.0 ppm. The area of the signal of HEA, that of the signal of CA, and that of the signal of EHA were 158.2, 7.9, and 9.1, respectively. Accordingly, the molar ratio of HEA/CA/EHA was calculated to be 96/2/2. The peak assignment described above is in a good agreement with that reported in a previous work [7,11].

2. Observation of Phase Transition of P(HEA-CA-EHA) in Aqueous Phase

Fig. 3 shows the temperature-dependent turbidity change of the solution of P(HEA-CA-EHA) and the mixture solution of P(HEA-CA-EHA) and alginate. The solution of P(HEA-CA-EHA) was clear in 20 ℃-27 ℃, and it began to be turbid around 28 ℃. The copolymerization of HEA with a non-polar monomer (e.g., methyl methacrylate) is known to produce a thermosensitive polymer having a lower critical solution temperature (LCST) [12]. In fact, P(HEA-CA-EHA) showed an LCST in an aqueous phase [7]. The copolymer chains will be dehydrated upon being heated and they will change their configuration from an extended form to a contracted one due to the hydrophobic interaction among CA residues. As a result, the copolymer chains will aggregate into insoluble particles, accounting for why the copolymer solutions became turbid as the temperature increased. On the other hand, the mixture solution of P(HEA-CA-EHA) and alginate was clear in the temperature range of 20 ℃-25 ℃, and it began to become turbid around 26 ℃. However, the mixture solution became slowly turbid and the rate of turbidity increase was obviously less than that of the copolymer solution containing alginate. There will be no electrostatic interaction between the copolymer and alginate because both of them are electrostatically neutral. There may be a physical entanglement between two kinds of polymers due to their long chains. In this circumstance, alginate could hinder the thermal contraction of P(HEA-CA-EHA) chains.

This could explain the reason why the thermo-sensitivity of the copolymer was lower in the presence of alginate.

3. Determination of CA Residues Dimerization of P(HEA-CA-EHA)

Fig. 4 shows the photo-dimerization degree of the CA residues of P(HEA-CA-EHA) in distilled water with and without alginate. The dimerization degree of P(HEA-CA-EHA) increased to 88.4% during the 90 min-irradiation of 365 nm. Coumarin is known to be dimerized to form a cyclobutane bridge under the irradiation of a UV light [13]. The dimerization decreased to 69% during the 90 min-irradiation of 254 nm. It is also known that the dimer is cleaved under the irradiation of a shorter UV light [13,14]. The profile of the dimerization degree of P(HEA-CA-EHA) with alginate was similar to that of the dimerization degree of P(HEA-CA-EHA) without algi-

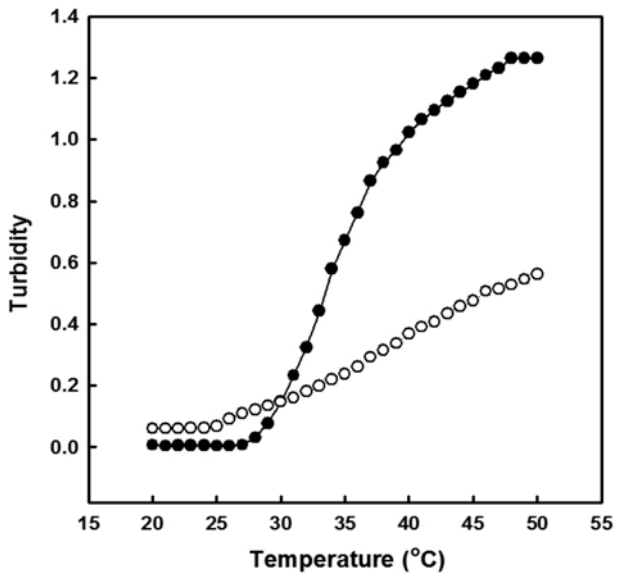

Fig. 3. Temperature-dependent turbidity change of P(HEA-CA-EHA) solution (●) and P(HEA-CA-EHA)/alginate mixture solution (○).

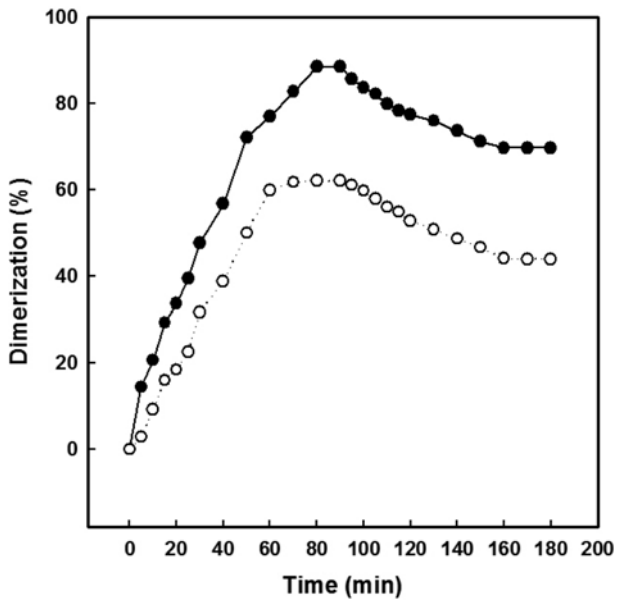

Fig. 4. Photo-dimerization degree of CA residues of P(HEA-CA-EHA) in distilled water with (○) and without (●) alginate.

nate. However, the dimerization degree of P(HEA-CA-EHA) with alginate was somewhat less than that of the copolymer without alginate. Alginate can absorb UV light and it can diminish the intensity of UV light available to the copolymer. In addition, alginate can be entangled with P(HEA-CA-EHA) and it can hinder the configurational change of the copolymer. As a result, the dimerization of the CA residues can be hindered due to the restriction in the configurational change. Although the dimerization was somewhat suppressed by alginate, it can be said that it could readily take place in the presence of the polysaccharide.

4. Characterization of Microspheres

The equation of a standard curve for CA was Y=0.8638 X+0.0203 (R^2=0.9994), where Y is the absorbance at 320 nm and X is the concentration of CA solution in 2 mg/ml. Using the equation and the absorbance of the solution obtained by dissolving alginate/P(HEA-CA-EHA) bead in PBS, the amount of CA residues contained in 10 mg of alginate/P(HEA-CA-EHA) bead was calculated to be 0.058 mg, which corresponds to 0.00019 mmol. Since the molar ratio of HEA/CA/EHA was 96.11/2.05/1.84, the molar amounts of HEA residue and EHA residue were calculated to be 0.00908 mmol and 0.000017 mmol, respectively. Accordingly, the masses of HEA and EHA were calculated to be 1.054 mg and 0.032 mg, respectively. Therefore, the mass of P(HEA-CA-EHA) contained in 10 mg of alginate/P(HEA-CA-EHA) bead was 1.144 mg (1.054 mg+0.058 mg +0.032 mg) and the content of the copolymer in the bead was calculated to be 11.44%. The weight ratio of alginate/P(HEA-CA-EHA) in the mixture solution used for the preparation of microspheres was 50 : 50. When the microspheres were washed with acetone, the copolymer could be washed out because it was not chemically cross-linked but physically entangled with photo cross-linked alginate. This may account for why the weight ratio of alginate/P(HEA-CA-EHA) in the microsphere (88.6/11.4) was much different from that of alginate/P(HEA-CA-EHA) in the mixture solution (50/50).

Fig. 5 shows the SEM photos of alginate microspheres and alginate/P(HEA-CA-EHA) microspheres. The particles were almost spherical and the diameter was less than 2 μm. Since the particles were prepared using the water droplets of W/O emulsion as a template, their shape will resemble the droplets (sphere) and their size will fall within the size range of the droplets. In fact, the droplets on the optical microphotograph were spherical and their diameter was a few micrometers. The shape and the size of alginate/P(HEA-CA-EHA) microsphere seem not to be markedly different from those of alginate microsphere. Since the microspheres were formed in the template of water droplets of W/O emulsion, their shape and the size will predominantly depend on those of water droplets. In fact, according to the photo micrographs, the inclusion of P(HEA-CA-EHA) in the water phase had little effect on the shape and the size of the water droplets. This may account for why the inclusion of P(HEA-CA-EHA) did not have a significant effect on the shape and the size of the microspheres.

5. Effect of UV Irradiation on Release from Microsphere

Fig. 6(a) shows the release profile of FITC-dextran from UV (365 nm)-treated alginate microsphere and UV (365 nm and 254 nm)-treated alginate microsphere. The release degree rapidly increased for the first 1 hr and then it increased slowly for the rest period. The saturated increase in release degree is commonly found with a monolithic type of particle (e.g., microsphere) [15,16]. There was no marked

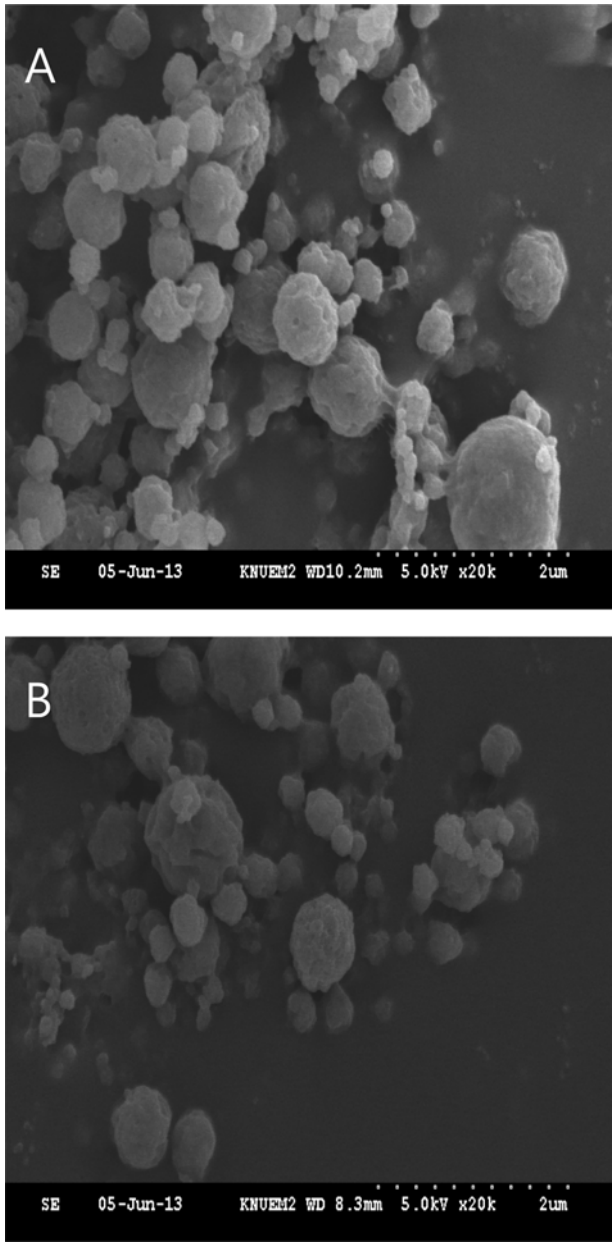

Fig. 5. SEM photos of alginate microspheres (a) and alginate/P(HEA-CA-EHA) microspheres (b).

difference in the release degree between two kinds of microsphere, and the maximum release degree was around 65%. Alginate has no photo-reactive group so the UV irradiations would have little effect on the release degree from alginate bead. Fig. 6(b) shows the release profile of FITC-dextran from UV (365 nm)-treated alginate/P(HEA-CA-EHA) microsphere and UV (365 nm and 254 nm)-treated alginate/P(HEA-CA-EHA) microsphere. The release degrees increased in a saturation manner and the release profiles resemble those of alginate microspheres. UV (365 nm and 254 nm)-treated alginate/P(HEA-CA-EHA) microsphere exhibited a higher release degree than UV (365 nm)-treated one. For example, the maximum release degree of UV (365 nm and 254 nm)-treated alginate/P(HEA-CA-EHA) microsphere was 78% and that of UV (365 nm)-treated alginate/P(HEA-CA-EHA) microsphere was 66%. The dimers of

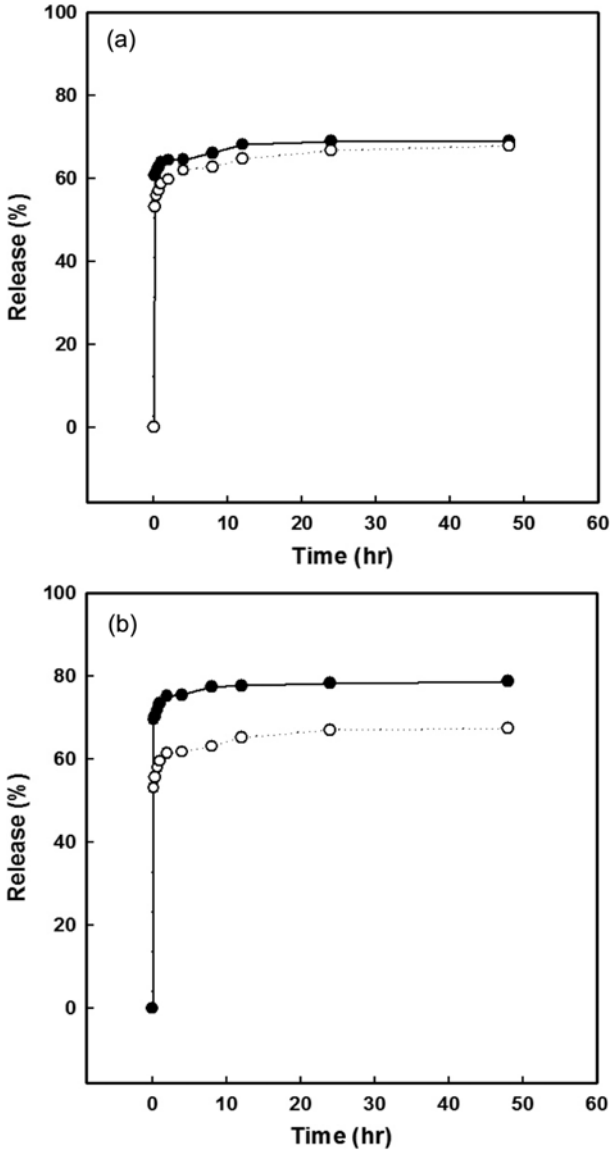

Fig. 6. Release profile of FITC-dextran from UV (365 nm)-treated microsphere (○) and UV (365 nm and 254 nm)-treated microsphere (●). Panel A is the release profile from alginate microsphere and panel B is the release profile from alginate/P(HEA-CA-EHA) microsphere.

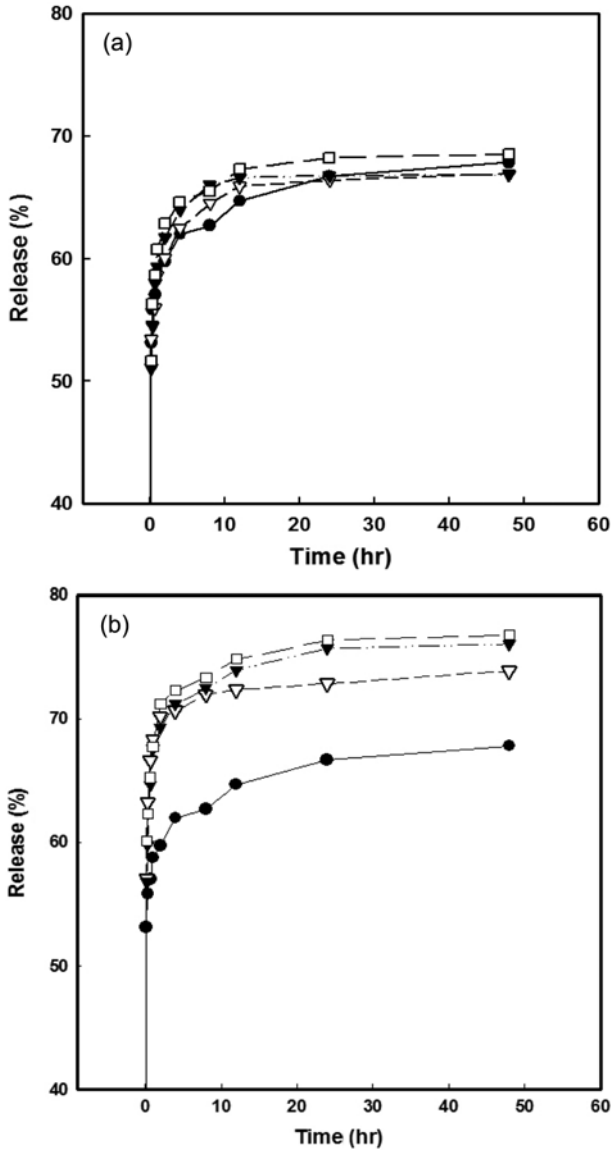

Fig. 7. Release profile of FITC-dextran from UV (365 nm)-treated alginate microsphere (Panel A) and UV (365 nm)-treated alginate/P(HEA-CA-EHA) microsphere (Panel B) at the temperature of 21 ºC (●), 27 ºC (▽), 30 ºC (▲), and 37 ºC (□).

CA residues were reported to be cleaved under the irradiation of UV (254 nm). In fact, the dimers were readily de-dimerized in the presence of alginate under the irradiation of UV (254 nm) (Fig. 4). Accordingly, the UV (254 nm) irradiation would decrease the cross-linking density of alginate/P(HEA-CA-EHA) microspheres and promote the release from them.

6. Effect of Temperature on Release from Microsphere

Fig. 7(a) shows the release profile of FITC-dextran from UV (365 nm)-treated alginate microspheres at the temperature of 21 ºC, 27 ºC, 30 ºC, and 37 ºC. The release degrees increased with time lapse in a saturation manner, and no marked difference in the release degree was observed among the microspheres contained in the release media of different temperatures. Alginate is not temperature-responsive and its chains hardly change their configuration with respect to the temperature change of medium. So, the configurational change can be excluded from the factors affecting the release degree. A major factor would be the diffusivity of diffusate (FITC dextran) through the microsphere matrix. Due to the temperature-insensitivity of alginate, the porosity and the pore size of alginate microspheres would hardly change with the temperature change. Thus, the diffusivity will depend mainly on the diffusion coefficient of FITC-dextran in aqueous medium within the microspheres. It is known that the diffusion coefficient is proportional to the medium temperature [17]. Accordingly, the release degree at a given time will increase with increasing the temperature. However, the release degree was almost the same regardless of the absolute temperature of medium. It is believed that the temperature range was not wide enough to give an appreciable difference in the release degree. Fig. 7(b) shows the

release profile of FITC-dextran from UV (365 nm)-treated alginate/(HEA-CA-EHA) microspheres at the temperature of 21 ºC, 27 ºC, 30 ºC, and 37 ºC. There was no marked difference in the release degree among the microspheres exposed to different temperatures. P(HEA-CA-EHA) likely to act as a thermal valve in the matrix of the microspheres and to control the release in response to the temperature change of medium (21 ºC to 37 ºC), because the copolymer exhibited a lower critical solution temperature around 27 ºC (Fig. 3). However, the temperature-sensitivity of the copolymer was lower when the copolymer co-existed with alginate (Fig. 3). Thus, the temperature-sensitivity of the copolymer in the alginate microsphere would not be enough for the copolymer to act as a thermal valve. Furthermore, the copolymers would be cross-linked in the alginate microspheres and form an interpenetrating network with alginate because the microspheres were UV (365 nm)-treated and the CA residues of the copolymer would be dimerized. So the thermally induced configurational change of the copolymer chains would be restricted due to their physical entanglement with alginate chains and their intermolecular photo cross-linkage. In this circumstance, P(HEA-CA-EHA) could hardly act as a thermal valve in the matrix of the microspheres and hardly control the release in response to the temperature change of medium. In our previous works, ploy(N-isopropylacrylamide)s (PNIPAMs), a well-known temperature-sensitive polymer, were contained in the matrix of alginate beads by a physical inclusion [18,19] and a chemical attachment [18,19]. The alginate bead containing PNIPAM exhibited a controlled release in response to the temperature change of release medium. Even though PNIPAMs co-existed with alginate, they were not cross-linked in the alginate bead and they could change their configuration without a restriction in response to temperature change. This may account for why the UV (365 nm)-treated alginate/P(HEA-CA-EHA) microspheres were not sensitive to the temperature change of the medium, but the alginate/PNIPAM beads were sensitive to the temperature change.

CONCLUSIONS

Alginate microspheres incorporating poly(hydroxyethyl acrylate-co-coumaryl acrylate-co-2-ethylhexyl acrylate) (P(HEA-CA-EHA)) were prepared as a UV irradiation-responsive and a temperature-responsive drug carrier. The microspheres were prepared using the water droplets of W/O emulsion as a template and Ca^{2+} as a cross-linker, and then subjected to UV (365 nm) irradiation for the dimerization of the CA residues of the copolymer. UV (254 nm) irradiation promoted the release of FITC-dextran from the microspheres, possibly due to the photo-cleavage of the dimers of the CA residues. However, the temperature change had little effect on the release degree in the range of 21 ºC to 37 ºC. The thermally induced configurational change of P(HEA-CA-EHA) seemed to be restricted, possibly because the copolymer chains were photo cross-linked. The microspheres prepared in the present study might be used as a photo-responsive drug carrier.

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