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Potential application of poly(*N*-isopropylacrylamide) gel containing polymeric micelles to drug delivery systems

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Abstract

We have investigated rapidly thermo-responsive NIPA gel containing polymer surfactant PMDP (NIPA-PMDP gel) as a potential drug carrier using (+)-L-ascorbic acid as a model drug. In the NIPA-PMDP gel system micelles of polymer surfactant PMDP are trapped by the entanglement of polymer chains inside the gel networks. Therefore, in principle the gel system tightly stores targeted drug in the micelles and rapidly releases controlled amount of the drug by switching on–off of external stimuli such as temperature or infrared laser beam. In our investigation on release profile, the NIPA-PMDP gel system showed completely different releasing behavior from that of the conventional NIPA gel. The NIPA-PMDP gel released rapidly all loaded (+)-L-ascorbic acid above the phase transition temperature (ca. 34 °C), while slowly released the corresponding amount of the drug below the temperature. In contrast, the conventional NIPA gel released more slowly limited amount of the drug above the phase transition temperature while similarly did to the NIPA-PMDP gel below the temperature. The release profile of the NIPA-PMDP gel seems to be governed by only kinetics of volume phase transition of the gel network but not by the hydrophobic domains of the micelles probably because of too hydrophilic nature of (+)-L-ascorbic acid.

Keywords: Thermoresponsive gel; Poly(*N*-isopropylacrylamide) (NIPA) gel; Polymer surfactant; Volume phase transition; Drug delivery system

1. Introduction

Poly(*N*-isopropylacrylamide) (NIPA) gel has attracted considerable attention from both academic and technological aspects [1–15]. NIPA gel undergoes an abrupt volume change at the phase transition temperature (ca. 34 °C) [1]. The abrupt volume change can be utilized in promising application of drug delivery systems [9–15]. Several strategies have been reported to realize much more rapid volume change of NIPA gels for better application of them [5–8]. Recently we have created NIPA gel system containing polymer surfactant poly(2-(methacryloyloxyl)decylphosphate) (PMDP) (cf. Scheme 1) [16,19] and have studied on bimorph-structured gel actuators [17]. We have also succeeded in synthesis of cylindrical microgels of the system [18]. The gel system shows rapid volume change by stimulus of temperature as well as laser beam irradiation [16]. Structurally the gel system contains the trapped micelles of PMDP inside the NIPA networks. Therefore, at least in principle the gel system tightly stores targeted drug in the micelles and rapidly releases controlled amount of the drug by switching on–off of external stimuli such as temperature or infrared laser beam. Herein we report on controlled-releasing profile of the NIPA-PMDP gel system using (+)-L-ascorbic acid and temperature as a targeted drug and a stimulus, respectively.

2. Materials and methods

Cylindrical NIPA-PMDP and NIPA gels were synthesized according to the procedure previously reported elsewhere [16]. The NIPA-based gels were synthesized by a free-radical polymerization as follows: 0.044 g of PMDP, 0.87 g of NIPA (cf. Scheme 1), 0.014 g of *N*,*N*′-methylenebisacrylamide (MBA), and 0.013 g of ammonium persulfate (APS) were dissolved in 8.5 g of deionized water. The solution was adjusted to pH 6 using 0.93 g of 0.1 M NaOH solution, then degassed and polymerized at 4 °C by the addition of 24 μl of tetramethylenediamine (TEMED). Polymerizations were carried out

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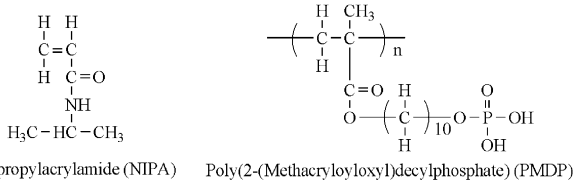

Scheme 1. Chemical structures of NIPA monomer and polymer surfactant PMDP.

in 1.3 mm-capillaries. The resulting NIPA-PMDP gels were repeatedly washed by immersion in pure water for several days. The NIPA gels were similarly synthesized but without PMDP.

Dye-solubilization experiment was carried out to confirm the presence of PMDP micelles in the gel. Yellow AB was chosen as an oil-soluble dye which is insoluble in water. Colors of the gels with and without addition of the Yellow AB were observed and recorded by an optical microscope (Olympus SZX7) with a digital camera.

Release profiles of the model drug from the gels were preliminarily measured as follows: cylindrical NIPA-PMDP or NIPA gels with initial size of 1.7 mm diameter × 9.2 mm length were used for measurements of the release profiles. The cylindrical gels were immersed in the solution of (+)-L-ascorbic acid (0.28 wt.%) for 24 h at 9 °C to load the model drug. Then the gels were washed by rinsing to remove the model drug adhering on surface of the gels. The experiments of release profile were performed in a quartz cell (1 cm × 1 cm) filled with pure water at room temperature (24 °C) and above the phase transition temperature (39–46 °C). The quartz cell in which the gels immersed was heated by thermoelectric heating/cooling unit (Netsu Denshi Thermomodule controller, MT862-04C12). The solution in the quartz cell was employed at a time interval for measurement of ultraviolet spectra by a spectrophotometer (Hitachi U-3010). The quartz cell was returned to the temperature-controlled water bath to keep it at the releasing temperature. The method should be improved further to keep the same temperature on UV measurement as that in water bath. The (+)-L-ascorbic acid has strong absorption at 205 nm of wavelength. Therefore, intensity of the absorption at 205 nm of wavelength has been measured for the solution in which the gel immersed. Finally cumulative amount of the (+)-L-ascorbic acid that the gel released was calculated by calibration with a standard concentration curve. The time-dependant cumulative amounts were normalized by the final cumulative one in the UV measurement.

After the preliminary investigation the release profiles were measured by HPLC technique under relatively well-controlled condition. The typical procedure was as follows: Cylindrical NIPA-PMDP gels with initial size of 1.7 mm diameter × 9.2 mm length were immersed in the solution of (+)-L-ascorbic acid (0.28 wt.%) for 5 days at 9 °C to load the model drug. Then the gels were washed by rinsing to remove the model drug adhering on the surface of the gels. The experiments of release profile were performed in a bottle filled with 10 g of pure water. The bottle in which the gels immersed was set in temperature-controllable (±0.1 °C) water-bath (EYELA NTT-2000). The solution in the bottle was sampled at a certain time interval at 27 and 40 °C, respectively. The sampled solution was measured by a HPLC analytic system. The HPLC chromatographic conditions were as follows: HPLC analytic system, Hitachi ELITE LaChrom; ODS column at 40 °C; flow rate, 1 ml/min; eluent, distilled water (HPLC grade); wavelength of detection, 205 nm. Cumulative amount (mg) of the (+)-L-ascorbic acid that the gel has released was calculated by calibration with a standard concentration curve which was prepared using chromatographic peak at retention time of 1.28. In the HPLC method the time-dependant cumulative amount was not normalized.

3. Results and discussion

As previously reported [16], the NIPA-PMDP gel shows five- and four-fold greater water-absorbencies than simple NIPA gel in pure water and in 0.15 M NaCl solution, respectively. And the phase transition temperature of the NIPA-PMDP gel was interestingly comparable to that of the conventional NIPA gel, both in pure water and in 0.15 M NaCl solution. It is important to note that the NIPA gel has been extensively studied as a candidate of DDS mainly because its transition temperature is ca. 34 °C, which is comparable to body temperatures [12].

The NIPA-PMDP gel also shows significantly rapid volume change (ΔV%) than that of NIPA gel at 43 °C [16]. The NIPA-PMDP gel shows ΔV% of 88% within 30 min, and subsequently collapsed within 120 min; in contrast, the NIPA gel showed only 24% within 30 min, and did not attain the completely collapsed state within the experimental time (2 h). The rapid volume phase transition of the NIPA-PMDP gel is reproducible, reversible and repeatable. No release of PMDP molecule from the NIPA-PMDP gel system is observed during the reversible volume change, which is confirmed by ultraviolet absorption spectra [16]. The colorless NIPA-PMDP gel (left side of Fig. 1) solubilizes an oil-soluble dye, Yellow AB, which is hydrophobic crystal and insoluble in water. The Yellow AB-solubilized NIPA-PMDP gel clearly showed yellowish color, as shown in right side of Fig. 1. Furthermore the NIPA gel did not show the yellowish color, as shown in Fig. 2, even when the gel was immersed in the

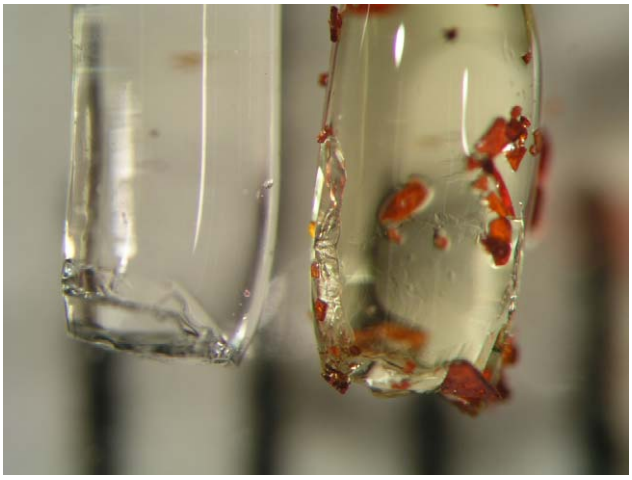

Fig. 1. Cylindrical NIPA-PMDP gels with (right) and without (left) oil-soluble dye Yellow AB. Fine crystals of Yellow AB are attached to the gel in the right side figure.