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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...
Scheme 1. Chemical structures of NIPA monomer and polymer surfactant PMDP.
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 x 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 °C 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-fold 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

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Figure 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.
The NIPA gel showed only 24% within 30 min, and did not attain the completely collapsed state within the experimental time (2 hr). 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 Figure 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 Figure 1. Furthermore the NIPA gel did not show the yellowish color, as shown in Figure 2, even when the gel was immersed in the water containing the Yellow AB powder. These results indicate that PMDP forms micelles within the NIPA gel network, and the micelles of polymer surfactant are trapped inside the gel networks, as schematically illustrated in Figure 3.

Accordingly we can suggest novel drug delivery system by using the NIPA-PMDP gel. Theoretically the NIPA-PMDP 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. The release profile may be completely different from the conventional NIPA gel.
phase transition temperature while gradually released all loaded drug below the temperature (Figure 4). The slow release above the transition temperature is well interpreted by the formation of a skin-type barrier which is less permeable to the drug [12]. On the other hand, the NIPA-PMDP gel rapidly released all loaded (+)-L-ascorbic acid above the phase transition temperature (ca. 34 °C), while showed slower releasing profile which is similar to that of the NIPA gel below the phase transition temperature (Figure 5). The release profile of the NIPA-PMDP measured by the HPLC analytic technique was shown in Figure 6. The NIPA-PMDP gel released the L(+)-ascorbic acid slowly and gradually with time at 27 °C which is lower than the phase transition temperature, 34 °C (Figure 6). The gel did not stop the release within the investigated time scale. On the other hand, the gel rapidly release the drug and finished the release within 10 min at 40 °C which is higher than the phase transition temperature. It is noted that, first the loading amount of the drug in the single gel was not exactly the same, and secondly the concentration of the sampled solution was somehow different from that of the completely mixed solution of the released drug. Therefore the experimental method needs further improvement to probe precisely and quantitatively the release profile of the NIPA-PMDP gels. Although some differences induced methodologically were observed in detail, the releasing trend was quite similar each other in Figures 5 and 6.

The rapid release above the transition temperature was explained by the rapid volume phase transition of the gel system [16], as shown in Figure 7. The NIPA-PMDP gel showed drastic volume change during the phase transition while the NiPa gel showed much less volume change at the same temperature range since well-known skin formation. The difference of release profiles between the NIPA and the NIPA-PMDP gels above the temperature exactly reflected the difference of the volume change during the phase transition [16]. The similar release profile below the transition temperature was suggested that the
(+)-L-ascorbic acid (cf. Scheme 2) is loaded inside the NIPA-PMDP gel network but outside the micelles of the polymer surfactant PMDP since the drug is highly hydrophilic, and the inner domain of the micelles is highly hydrophobic.

It is noted that the release profile should be investigated in physiologic media, and the phase transition temperature of the NIPA-PMDP gel should be lifted above body temperature in the case of practical applications.

In conclusion, the rapidly thermo-responsive NIPA-PMDP gel system, in which micelles of polymer surfactant PMDP are trapped within the gel network, showed completely different releasing behavior from the conventional NIPA gel. The NIPA-PMDP gel rapidly released 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 more slowly released limited amount of the drug above the temperature while similarly released with the NIPA-PMDP gel below the temperature. The release profile of the NIPA-PMDP gel may be governed by only the 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 the (+)-L-ascorbic acid. The NIPA-PMDP gel system may be suitable for a drug delivery system which rapidly release controlled amount of some hydrophobic drug by on-off of external stimuli such as infrared laser irradiation.

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