Controlled Release of Vitamin E from Thermo-Responsive Polymeric Physico-Gel

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Thermo-sensitive copolymer consists of poly(2-ethoxyethyl vinyl ether) and poly(hydroxyethyl vinyl ether) (EOVE200–HOVE400), whose sol–gel transition temperature was 20.5 °C, was synthesized and its applicability to a drug delivery system was examined. Vitamin E (VE) was enclosed in EOVE200–HOVE400 and the release of VE was measured by varying the temperature 10⇔30 °C. There was no release of VE from EOVE200–HOVE400 at 30 °C, while VE was released when the temperature was reduced to 10 °C.

Key words thermo-sensitive copolymer; drug delivery system; vitamin E; sol–gel transition; polymeric micelle

It is important to establish a drug delivery system (DDS) that ensures high efficacy and minimal side effects of a medicine. The applicability of polymer gel has been studied for a thermo- or pH-responsive DDS.[1,2] Poly(ethylene glycol),[3] poly(*N*-isopropylacrylamide),[4] poly(methyl vinyl ether)[5] and methyl cellulose derivatives[6] are known as a thermo-sensitive polymers, which are based on the swelling and contraction of polymers as the temperature changes. Poly(*N*-isopropylacrylamide) has been widely studied, and the practical use of poly(*N*-isopropylacrylamide) in a cell-culture laboratory dish was reported.[7—9] The synthetic technique is important to obtain a high quality polymer. Recently, the development of a living polymerization technique[10] has progressed. Thermo-sensitive polymers synthesized by a living cationic polymerization process have some advantages[11]: (1) the distribution range of the molecular weight is narrow, having a highly sensitive thermo-response; (2) thermo-hysteresis is small; (3) there are no side products yielded, which is very useful in clinical practice, since polymers with low molecular weight are harmful to the human body. Aoshima *et al.*[12,13] synthesized a thermo-sensitive polymer, poly(2-ethoxyethyl vinyl ether) (EOVE200), by living cationic polymerization. EOVE200 sharply undergoes sol–gel transition at 21.2 °C: demonstrating a semitransparent sol state below 21.2 °C and an opaque gel state above 21.2 °C. Furthermore, copolymer EOVE200–HOVE400 was synthesized,[14] where poly(hydroxyethyl vinyl ether) (HOVE400) is a hydrophilic segment. Thermo-sensitive segment EOVE200 brings about the hydrophilic-hydrophobic transition at the lower critical solution temperature (LCST), while hydrophilic segment HOVE400 is independent of temperature. Namely, thermo-sensitive copolymer consists of hydrophilic and hydrophobic segments above the LCST, whose structure is similar to a surfactant. Thus, EOVE200–HOVE400 spontaneously forms polymeric micelles above the LCST and enters a gel-state.[15] In general, the core space of polymeric micelles is highly hydrophobic.[16] The application of polymeric micelles to a microreservoir for hydrophobic compounds has been studied.[16] On the other hand, the application of polymer gel to a thermo-responsive DDS has been carried out.[1] The release of drug from thermo-sensitive crystalline complexes has also been reported.[17—20] Many studies are related to drug release when the temperature is raised. In this study, we synthesized thermo-sensitive copolymer EOVE200–HOVE400 and examined its applicability to a drug delivery system. As a result, EOVE200–HOVE400 released vitamin E (VE) when the temperature was reduced, leading to a better use of VE. We report the results herein.

Thermo-sensitive copolymer EOVE200–HOVE400 was synthesized according to the living cationic polymerization.[15] The transition temperature of 20 wt% EOVE200–HOVE400 was 20.5 °C. Visual observations of EOVE200–HOVE400 at 10 and 30 °C are shown in Fig. 1. EOVE200–HOVE400 changed from a transparent sol-state to a transparent gel-state at the transition temperature. The transparent gel-state of EOVE200–HOVE400 is based on polymeric micellization.[15]

α-Tocopherol (Vitamin E, VE), which is a medicine for a chilblains, frostbite or cold disease, was dissolved in water–ethanol (1 : 1 v/v%) mixed solvent because of the insolubility of VE in water and 2 wt% VE solution was obtained. The VE solution was added to the sol-state of 15 wt% EOVE200–HOVE400 at about 10 °C then stirred. Next, 1.0 g of sol of EOVE200–HOVE400 containing VE was put in the dialytic tube and gelatinized by blowing warm air. The sol–gel transition temperature of EOVE200–HOVE400 was reduced with increasing concentration of ethanol and had a minimum value at 35 wt% ethanol. This phenomenon is a cononsolvency.[21] In this study, the final concentration of ethanol in EOVE200–HOVE400 gel was 10 wt% taking the effect of ethanol and the solubility of VE into account. For the convenient determination of VE without dilution, 0.4 wt% final concentration of VE was used. The sol–gel transition temperature of EOVE200–HOVE400 was reduced to 18.2 °C by the addition of 10 wt% ethanol and 0.4 wt% VE, but there was no significant change in viscoelasticity. It

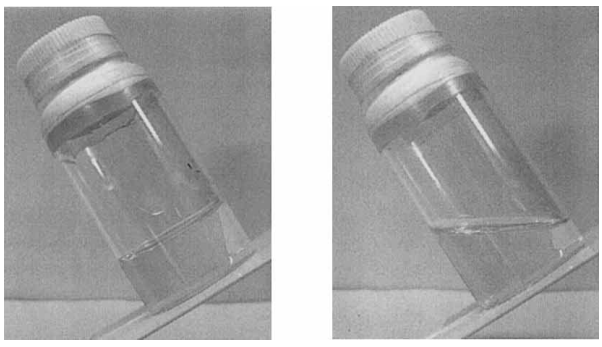

Fig. 1. Visual Observation of Sol and Gel States of EOVE200–HOVE400 at 10 and 30 °C, Respectively

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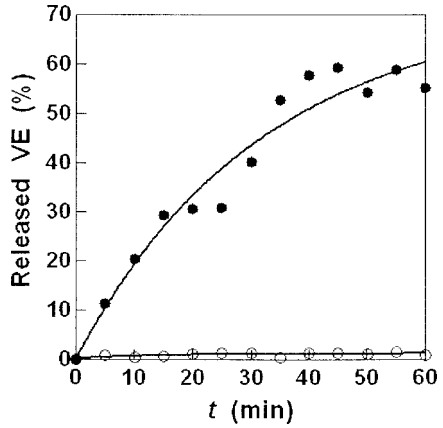

Fig. 2. Release Behavior of VE from EOVE200–HOVE400 at 10 °C (●) and 30 °C (○)

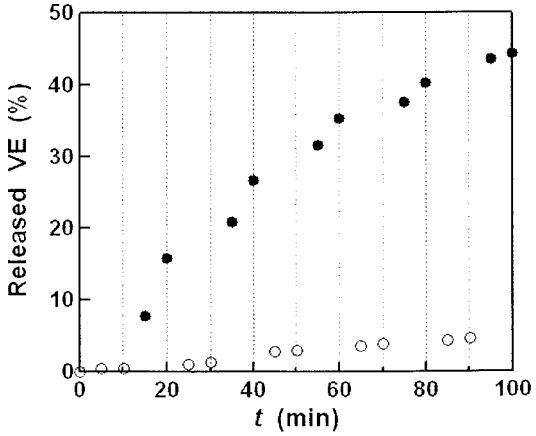

Fig. 3. Release Behavior of VE from EOVE200–HOVE400 with Repeated Changing of the Temperature from 30 °C (○)⇔10 °C (●)

was confirmed by the fluorescence method using 1,6-diphenyl-1,3,5-hexatriene (DPH) that VE was encapsulated into the core of EOVE200–HOVE400 polymeric micelles above the transition temperature. DPH is a fluorescent probe which reflects the hydrophobic micro-environment.[22] VE released from the sol-state EOVE200–HOVE400 through the dialysis tube to 300 ml of 10 wt% ethanolic water was fluorometrically determined. The wavelengths of excitation and emission were 290 and 320 nm, respectively.

The release behavior of VE from EOVE200–HOVE400 was examined in 10% ethanolic water at 10 and 30 °C, and the results are shown in Fig. 2. About 60% of VE was released from the sol-state of EOVE200–HOVE400 within 1 h at 10 °C, while VE was scarcely released from the gel-state of EOVE200–HOVE400 at 30 °C.

Next, a temperature-exchange experiment was repeatedly carried out using two vessels containing 10 and 30 °C test medium: the dialysis tube enclosed EOVE200–HOVE400 containing VE was removed from 30 °C medium then immersed in 10 °C medium, and this operation was repeated. The results at temperature 30⇔10 °C are shown in Fig. 3, where the ordinate is the total amount of VE released at 10 or 30 °C, respectively. There was no release of VE from EOVE200–HOVE400 at 30 °C. When the temperature was reduced to 10 °C, VE was released from EOVE200–HOVE400, and the release stopped when the temperature increased from 10 to 30 °C. The small amount of VE at 30 °C shown in Fig. 3 is a contamination from the 10 °C medium.

Many studies[1,3—6] with regard to a thermo-responsive DDS are related to drug release when the temperature is raised, which is based on the contraction of polymer at higher temperatures compared to the swollen state at lower temperatures. On the contrary, the characteristic controlled-releasability of EOVE200–HOVE400 is based on polymeric micellization above the LCST. In addition, the precise drug delivery function is the result of the narrow distribution of molecular weight and the small thermo-hysteresis of EOVE200–HOVE400. This is the first report with regard to the application of polymeric physico-gel and thermo-responsive VE product, which releases VE when the temperature is reduced. We conclude that the EOVE200–HOVE400 polymeric physico-gel containing VE may be a useful VE product. Furthermore, thermo-sensitive EOVE200–HOVE400, which releases drugs or chemical substances when the temperature is reduced, will be widely applicable not only in the pharmaceutical field but also in other fields.

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