Release Behavior from Hydrogen-Bonded Polymer Gels Prepared by Pressurization

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ABSTRACT: Our previous research showed that a simple ultra-high-pressure process made poly(vinyl alcohol) (PVA) solution into a macrogel and nanoparticles. To investigate the release properties of PVA hydrogels prepared by the ultra-high-pressure treatment, we prepared hydrogels containing model drugs by pressurizing a PVA solution with Alfa-G Hesperidin or Oil Blue N as a water-soluble or an oil-soluble model drug, respectively. In the case of the oil-soluble drug, an oil-in-water emulsion, Oil Blue N containing dodecane in a PVA solution, was used by homogenization before pressurization. The average diameter and the diameter distribution of oil droplets before and after the ultra-high-pressure treatment were almost the same. However, the PVA hydrogel prepared at 10,000 atm for 10 min exhibited the slowest release rate of model drugs. Thus, we found that the release rates of the model drugs from the PVA hydrogels were controlled by the degree of crosslinking in the resulting gels, which was determined from the operation parameters of the ultra-high-pressure treatment, such as the pressure, time, and concentration of the PVA solution. Therefore, an ultra-high-pressure process is promising for drug-carrier development because of the nonharmful simple preparation process. © 2010 Wiley Periodicals, Inc. J Appl Polym Sci 119: 2725–2729, 2011

Key words: diffusion; gels; hydrogels; hydrophilic polymers

INTRODUCTION

A considerable number of studies have been devoted to the study of the molecular assembly technology in the material processing field, such as in molecular machines,[1] carbon nanotubes for biological systems[2] and circuit wires,[3,4] and drug carriers.[5,6] Molecular assembly is organized by noncovalent bonding, such as electrostatic interaction, van der Waals forces, and hydrogen bonding. It is important for the formation of molecular assembles to control these interactions by changing intensive variables.[7–9] Therefore, we showed that pressure must also be available to control the intermolecular forces to generate molecular assembles. We found that a poly(vinyl alcohol) (PVA) solution turned into a macrogel or nanoparticles through a simple ultra-high-pressure process (10,000 atm for 10 min).[10] Our results demonstrate that ultra-high pressure induces hydrogen bonding in water that is strong enough to maintain microassemblies, such as gels and particles. In addition to the formation of gels and nanoparticles, we found that the swelling ratio of the gels and the size of nanoparticles were easily controlled by the operative parameters in an ultra-high-pressure process. Furthermore, the macrogel prepared by this process indicated discriminating elasticity, which was never seen in the conventional PVA hydrogels.

Hydrogels are used in a wide variety of applications as a soft material, including in soft contact lenses,[11] shock absorption materials,[12] and drug carriers.[13,14] So far, several articles have been written on the drug-release behavior from PVA hydrogels prepared by physical crosslinking[15,16] and chemical crosslinking.[17,18] In these reports, the authors have concluded that PVA hydrogels are suitable for drug delivery because of their excellent drug-release characteristics and biocompatibility. As the ultra-high-pressure process does not require any harmful compound for crosslinking, we remarked on the hydrogel prepared by an ultra-high-pressure process as a

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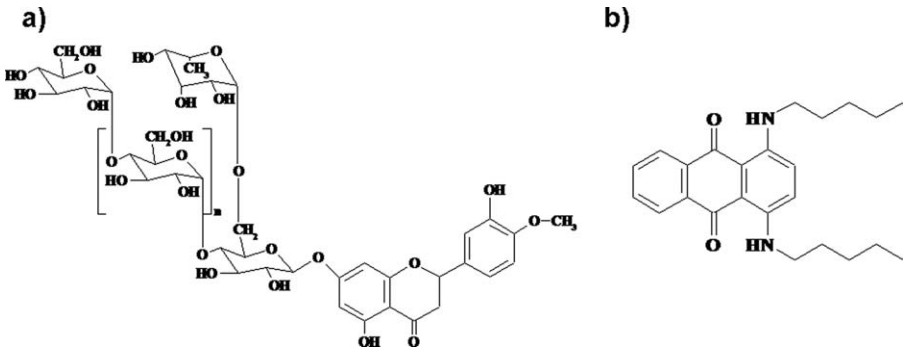

Figure 1 Chemical structures of the model drugs: (a) Alfa-G Hesperidin and (b) Oil Blue N.

drug carrier. That is why it is important to clarify the capability of controlled release from PVA hydrogels produced by an ultra-high-pressure process.

In this study, we prepared PVA hydrogels with a water-soluble or oil-soluble drug through an ultra-high-pressure process, and the drug-release behavior from the gels was investigated.

EXPERIMENTAL

Materials

PVA (99.85 mol % hydrolyzed) was used without further purification. This was kindly supplied by Kuraray Co., Ltd. (Osaka, Japan). We used Alfa-G Hesperidin and Oil Blue N as the water-soluble and oil-soluble model drugs, respectively. Alfa-G Hesperidin was kindly supplied by Hayashibara Biochemical Research Laboratory Co., Ltd. (Okayama, Japan). Oil Blue N was purchased from Sigma-Aldrich Japan Co. (Tokyo, Japan). The chemical structures of Alfa-G Hesperidin and Oil Blue N are shown in Figure 1.

Preparation of the cylindrical PVA hydrogels

PVA (10 or 20% w/v) aqueous solutions were prepared with an autoclave. A PVA aqueous solution mixed with a 10% w/v Alfa-G Hesperidin aqueous solution was treated under ultra-high pressure. The ultra-high-pressure apparatus was Dr. CHEF, which was made by Kobe Steel, Ltd. (Osaka, Japan). The treatment conditions were as follows: the ultra-high-pressure treatment condition was 6000–10,000 atm, the treatment time was 1–60 min, and the treatment temperature was kept at 313 K, at which no ice crystals were formed.[19] After the treatment, the prepared gels were cut into the desired shape. A representative photograph of a prepared gel is shown in Figure 2(a). The shape of gel was cylindrical. The length was 10 mm, and the diameter was 5 mm.

A dodecane solution dissolving 0.1% w/v Oil Blue N was mixed with a 10% w/v PVA aqueous solution. The solution was homogenized for 10 min at 6000 rpm to prepare oil-in-water (o/w) emulsions with a homogenizer. After that, the emulsion solution was treated under ultra-high pressure. The ultra-high-pressure treatments were carried out at 6000–10,000 atm for 1–60 min at 313 K. A typical prepared gel is shown in Figure 2(b). The diameter of the dodecane droplets was measured under a microscope before and after ultra-high-pressure treatment.

Evaluation of the model drug-release behavior from the gels

The release behavior of the water-soluble model drug from the PVA hydrogel was evaluated in ultrapure water. The hydrogel in the vial with ultrapure water was placed in a thermostated water bath at 303 K. The solution was shaken at 100 rpm to keep the concentration constant. Samples were withdrawn

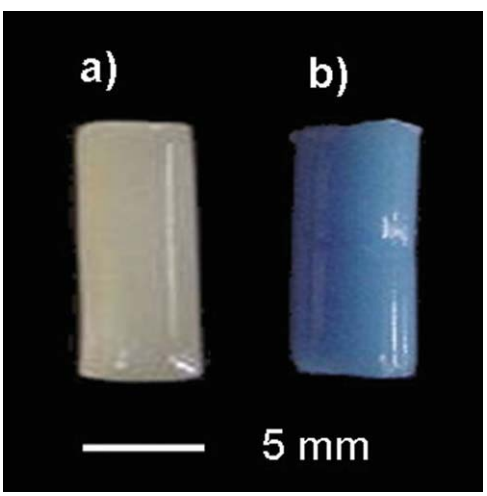

Figure 2 Photograph of the PVA gel prepared by ultra-high-pressure treatment (10,000 atm for 10 min at 313 K): (a) PVA gel with 5% w/v Alfa-G Hesperidin, the water-soluble model drug, with a PVA concentration of 10% w/v and (b) PVA gel with 0.1% w/v Oil Blue N, the oil-soluble model drug, with a PVA concentration of 10% w/v. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

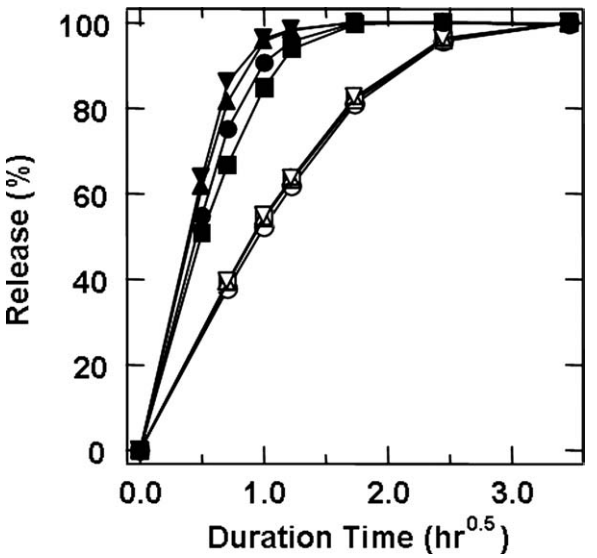

Figure 3 Release behavior of Alfa-G Hesperidin from the PVA hydrogels. A 5% w/v PVA solution with a 5% w/v Alfa-G Hesperidin solution was treated under the following conditions: (●) 10,000 atm for 10 min, (■) 9000 atm for 10 min, (▲) 8000 atm for 10 min, and (▼) 8000 atm for 20 min. A 10% w/v PVA solution with a 5% w/v Alfa-G Hesperidin solution was treated under the following conditions: (○) 10,000 atm for 10 min, (□) 9000 atm for 10 min, (△) 8000 atm for 10 min, and (▽) 8000 atm for 20 min.

at predetermined intervals to measure the amount of released Alfa-G Hesperidin. The concentration of Alfa-G Hesperidin in the samples was determined by measurement of the absorption at a wavelength of 282.5 nm with an ultraviolet–visible spectrophotometer (U-2000A, Hitachi, Ltd., Tokyo, Japan).

The release behavior of the oil-soluble model drug from the PVA hydrogel was evaluated in an ethanol solution.[20] The hydrogel in a vial with the ethanol solution was placed in a thermostated water bath at 303 K. The solution was shaken at 100 rpm to keep the concentration constant. The released Oil Blue N was determined by measurement of the concentration of Oil Blue N in the collected samples at predetermined intervals at 642.5 nm with the ultraviolet–visible spectrophotometer.

The release data were shown with a Higuchi plot, with the cumulative amount of released drug versus the square root of the duration time ($h^{0.5}$).[21] It was available with the estimation of an initial drug release rate because the release data in the early stages were proportional to the root of the duration time.

RESULTS AND DISCUSSION

Release behavior of Alfa-G Hesperidin from the gels

The PVA hydrogels, as shown in Figure 2(a), were obtained in the case that the PVA aqueous solution dissolving Alfa-G Hesperidin was treated under ultra-high pressure. The prepared PVA hydrogels were uniformly yellowish, which color was based on Alfa-G Hesperidin, so Alfa-G Hesperidin was homogeneously distributed in hydrogels. The PVA hydrogels with Alfa-G Hesperidin prepared in this study were as elastic and flexible as the gel without any solutes.

Figure 3 shows the release behavior of Alfa-G Hesperidin from the PVA hydrogels. We found that Alfa-G Hesperidin, the water-soluble model drug, was completely released from the 5% w/v PVA gel within about 3 h. However, the complete release of Alfa-G Hesperidin from the 10% w/v PVA gel took about 12 h. This delay in the release behavior of the water-soluble compound was caused by the dense polymer network in the 10% w/v PVA gel.

The release rate was estimated from the initial slopes in Figure 3 and is shown in Figure 4. The release rates from the hydrogels treated at higher pressure (9000–10,000 atm) were lower than that from the hydrogel treated under 8000 atm because the treatment at a higher pressure enhanced crosslinking in the polymer network and induced a more elastic and stronger hydrogel. However, the treatment time in the ultra-high-pressure process at 8000 atm hardly affected the release rates of Alfa-G Hesperidin. Generally, release behaviors are affected by the crosslinking density in the gels, which is derived from the swelling ratio of the gels. In our previous study, we found that the swelling ratio of PVA hydrogels prepared by ultrahigh pressurization decreased with increasing pressure and was constant when a fixed pressure (>6000 atm) was applied for more than 10 min.[10] Because these drug-release

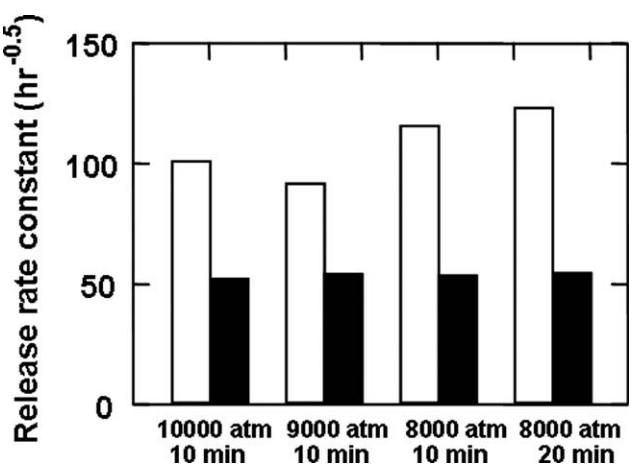

Figure 4 Release rate constants of Alfa-G Hesperidin from the PVA hydrogels derived from the initial slopes of the release curve of Alfa-G Hesperidin from the PVA hydrogels. The compositions of the gels were as follow: (white bar) 5% w/v PVA and 5% w/v Alfa-G Hesperidin and (black bar) 10% w/v PVA and 5% w/v Alfa-G Hesperidin.

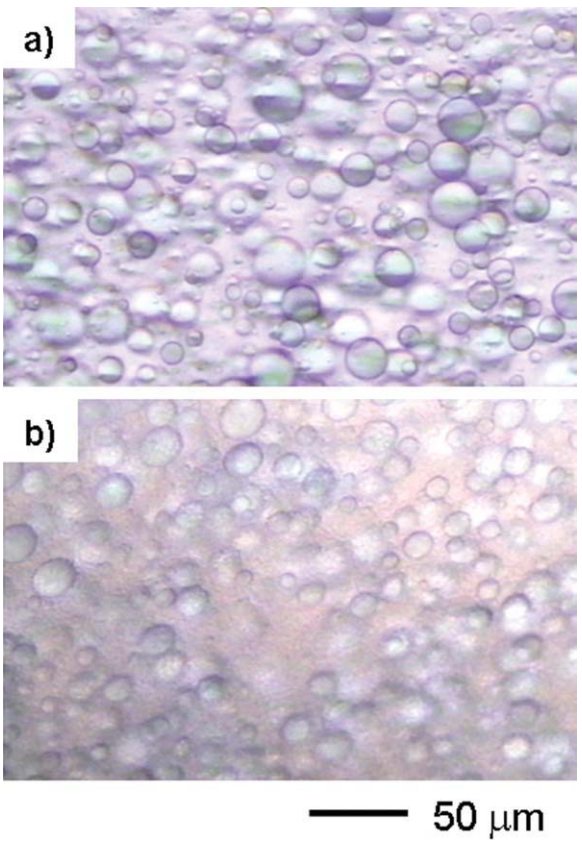

Figure 5 Photographs of o/w emulsion droplets: (a) in solution (before pressurization) and (b) in PVA hydrogel (after pressurization). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

behaviors indeed corresponded to the crosslinking state in the gels, the treatment pressure played a most important role in the operation parameters of the ultra-high-pressure treatment to control the release rate from the gel. The effect of PVA concentration on the release properties was found to be significant; the release rates from the 10% w/v PVA gels were approximately half of those from the 5% w/v PVA gels. From the results shown in Figures 3 and 4, the effects of the treatment pressure and treatment time on the release rate of Alfa-G Hesperidin were smaller than those of the PVA concentration.

Release behavior of Oil Blue N from the gels

The PVA hydrogel with dodecane droplets was obtained by ultra-high-pressure treatment [Fig. 2(b)]. Figure 5 shows the o/w emulsion droplets dissolving Oil Blue N in solution and that in the PVA hydrogel prepared by ultra-high-pressure treatment. Figure 6 shows the diameters and the coefficients of variation (CVs) of dodecane droplets before and after the ultra-high-pressure treatment. Dodecane droplets were stably dispersed in the media. According to Figure 6, the average diameter and the diameter distribution before and after the ultra-high-pressure treatment were almost the same. Under ultra-high pressure, the volumes of the oil and water phases seemed to be decreased, and the density and the concentration of the solution were enhanced. Such a condition may have involved the droplet instability through the interfacial tension change. In fact, however, we observed no droplet coalescence in the gels. This result suggests that a homogeneously

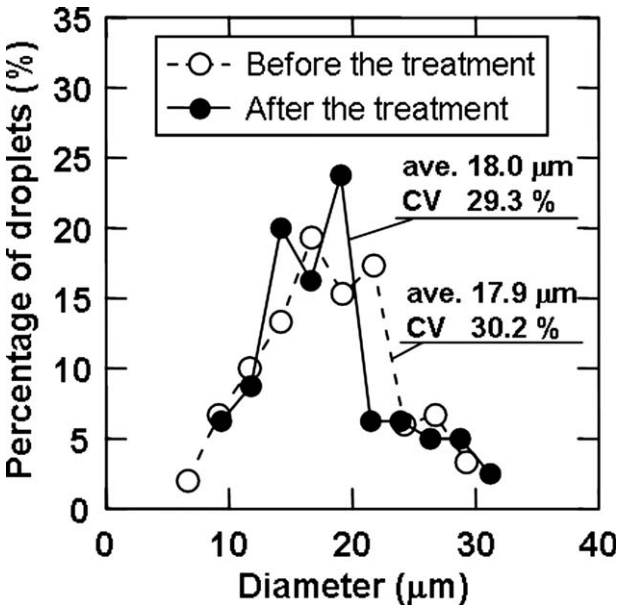

Figure 6 Diameter distributions of dodecane droplets before and after the ultra-high-pressure treatment.

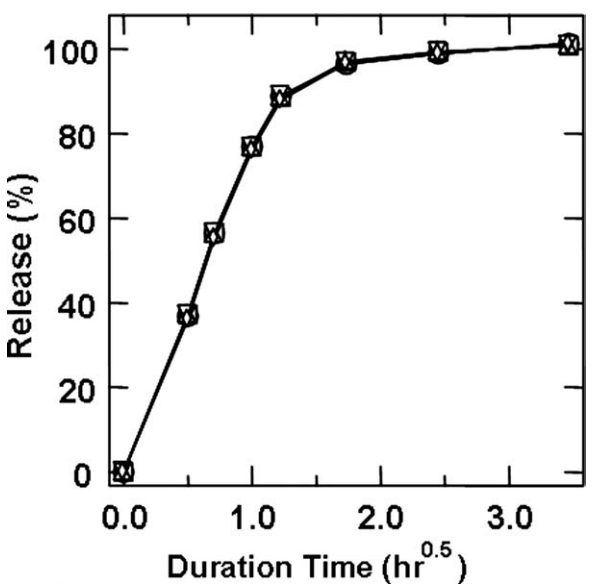

Figure 7 Release behavior of Oil Blue N from 10% w/v PVA hydrogels in ethanol. The pressurized conditions were (○) 10,000 atm for 10 min, (□) 9000 atm for 10 min, (△) 8000 atm for 10 min, (□) 8000 atm for 20 min, and (◇) 8000 atm for 60 min.

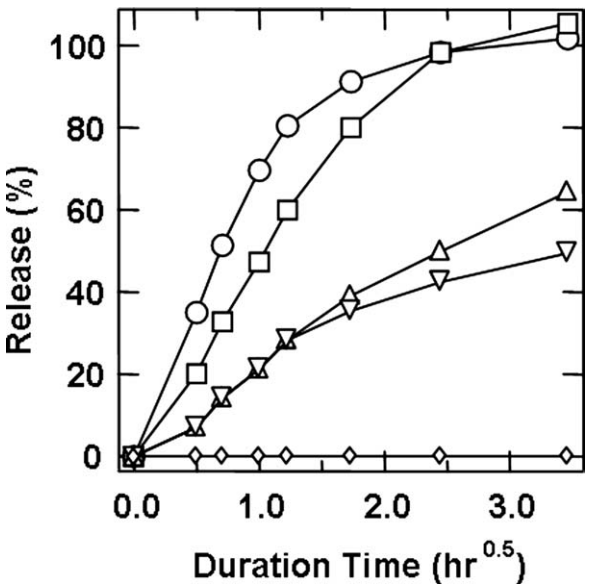

Figure 8 Effect of ethanol concentration on the release rates. All of the hydrogels were prepared by pressurization (treatment conditions: 10,000 atm for 10 min). The ethanol concentrations were as follows. (○) 100, (□) 75, (△) 50, (□) 25, and (◇) 0 wt %.

hydrophobic drug-dispersed hydrogel was prepared by an ultra-high-pressure process when a stable o/w emulsion was obtained in the PVA solution.

The release behavior of Oil Blue N is shown in Figure 7. The release behavior was almost the same over a wide range of treatment pressure and treatment time. The release rate from this PVA hydrogel was about 75 $h^{-0.5}$, which was slightly higher than that from the hydrogels. This difference in the release rate between the water-soluble and oil-soluble model drugs may suggest the diffusion resistance of a drug in PVA matrix. That is, Alfa-G Hesperidin was incorporated into the PVA hydrogel matrix by hydrogen bonding, which was formed between the hydroxyl groups of Alfa-G Hesperidin and those of PVA. Therefore, the release rate of the oil-soluble model drug from the PVA hydrogels was slightly higher than that of the water-soluble model drug.

In addition, the effects of ethanol concentration on the release rate of the model drug are shown in Figure 8. As shown in this figure, the release rate of Oil Blue N from the PVA hydrogel increased with increasing ethanol concentration in the solution. In the case when water (0 wt % ethanol) was used as the medium, no release of Oil Blue N was observed. According to the results shown in Figures 7 and 8, the diffusion of ethanol into the hydrogel was a predominant step for the release of the oil-soluble drug.

CONCLUSIONS

As the PVA solutions dissolving the water-soluble model drug or dispersing the oil-soluble model drug were treated under the ultra-high pressure, hydrogels were obtained. The release rate of each model drug from the PVA hydrogel was controlled by the operation parameters of the ultra-high-pressure treatment, such as the pressure, time, and concentration of the PVA solution. The average diameter and diameter distribution of dodecane droplets before and after the ultra-high-pressure treatment were almost the same. Thus, we expect this technique to be useful as a preparation technique for innocuous sustained-release materials.

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