Application of Syndiotacticity-Rich PVA Hydrogels Prepared at a Low Temperature to Thermo- and pH-Responsive Release Devices

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ABSTRACT: Three kinds of physically cross-linked syndiotacticity-rich poly(vinyl alcohol) (*s*-PVA) hydrogels were prepared at 0°C with use of the buffer solutions (BS) of pHs 4.0, 7.4, and 9.0. Three gels swelled at first and then began to shrink after 12 h when they were dipped in the same BS for preparation at higher temperature than 0°C. The release of Brilliant Blue (3 mg/1 mL) from the cylindrical gels prepared using BS of pH 7.4 was studied at 27, 37, and 47°C. Brilliant Blue has been released spending 4–12 h almost completely. The rate of release from the gel at temperatures of 27, 37, and 47°C became large with increasing temperature. The main factor on release of Brilliant Blue is not the contraction of gel, but swelling, because the degree of swelling (DS) became large with increasing temperatures for 27, 37, and 47°C. The rate of release from the gel (pH 4.0) was larger than that (pH 7.4) due to the increased DS of the hydrogel in early step at pH of 4.0. The apparent diffusion exponents of these releases at pH 7.4 evaluated from first 60% of the fractional release were lower than 0.45 due to the swelling during release. The exponent at pH 4.0 was 0.45 due to immediate swelling. The on-off of shrinking behavior of atactic PVA (*a*-PVA) hydrogel was observed under several temperature changes. The rate of release of Brilliant Blue at 5°C was lower than that at 27°C and no change was observed at 5°C after one on-off cycle. © 2000 John Wiley & Sons, Inc. J Appl Polym Sci 78: 41–46, 2000

Key words: hydrogel; *s*-PVA; Fickian diffusion; swelling; shrinking

INTRODUCTION

Many studies on drug delivery systems using polymer gel networks were reported.[1–4] Among them, hydrogels are of utility value because of its high water content.[5–12] Syndiotacticity-rich poly(vinyl alcohol) (*s*-PVA) hydrogels are more stable and the preparation is easier in comparison with atactic poly(vinyl alcohol) (*a*-PVA) hydrogels. The authors had thought that the characteristics might be applicable as a drug delivery system, and investigated on the release device using the *s*-PVA hydrogels prepared at 30°C.[13] These gels showed thermo- and pH-responsive release and the characteristics of Fickian diffusion (diffusion exponent: 0.40–0.50), however the perfect release of drug was not achieved within predetermined time. The behavior at elevated temperatures and several pHs of the *s*-PVA hydrogel prepared at 0°C were investigated. The gel was found to swell at first and then to shrink. We took advantage of the characteristics for the release. In this study, the perfect release was tried to realize using the characteristics of the swelling of hydrogel during

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Table I *s*-PVA Used

			Triad (%)		
DP	*s*-diad (%)		*I*	*H*	*S*
1850[a]	56.2[b]	57.4[c]	18.9[c]	47.3[c]	33.8[c]

[a] From intrinsic viscosity of acetylated PVA using $[\eta] = 56.3 \times 10^{-4} DP^{0.62}$ (benzene, 30°C).
[b] From infrared spectrum of film using *s*-diad (%) = $72.4 (D_{916}/D_{849})^{0.43}$
[c] From ^{1}H-NMR spectrum

release. The release of Brilliant Blue during swelling from the *s*-PVA hydrogels prepared at 0°C was studied at different temperatures (27–47°C) and pHs (4.0–7.4 at 37°C). Okano et al. have reported that poly(N-isopropylacrylamide-co-butylmethacrylate) is available for thermally on-off switching device for drug release.[14,15] The gel showed reversible swelling characteristics. The authors studied the response of the *s*-PVA hydrogel to the repeating temperature changes.

EXPERIMENTAL

Materials

The *s*-PVAs used are shown in Table I. They were prepared by the saponification of poly(vinyl trifluoroacetates) prepared by the radical polymerization of vinyl trifluoroacetate at 60°C. Brilliant Blue was purchased from Wako Pure Industries, Osaka, Japan.

Working Curves of Buffer Solution

The working curves for Brilliant Blue in each buffer solution with given pH were made by measuring the absorbance at the wavelength of 629 nm using an ultraviolet-visible spectrophotometer (Shimazu UV-160). The working curves obtained are showed in Figure 1.

Preparation of Cylindrical *s*-PVA Hydrogels Containing Brilliant Blue

The 0.1 g of *s*-PVA, 1 mL of each buffer solution of pH 4.0, 7.4, and 9.0, and 3 mg of Brilliant Blue were added to every test tube, each with the diameter of 1.0 cm. After the *s*-PVA was dissolved at 120°C, the test tubes were opened and then stopped with silicon plugs. The tubes were turned over to make cylindrical hydrogels. After that, the solutions were gelled at 0°C for 24 h. Thus, the cylindrical hydrogels of the diameter of 1.0 cm and length of 1.3 cm were obtained. The hydrogels without Brilliant Blue were also prepared. The gels prepared from the buffer solutions of pH 4.0, 7.4, and 9.0 are named 4.0-gel, 7.4-gel, and 9.0-gel.

Swelling Followed by Shrinking

The 7.4-gel gelled was placed in the buffer solution of pH 7.4 of a fixed temperature (0–50°C) and the swelling followed by shrinking with time of the gel was studied by weighing the gel at predetermined times (0–48 h). The swelling followed by shrinking with time for 4.0-gel, 7.4-gel, and 9.0-gel at 37°C were also studied.

Dissolution of Low-Molecular-Weight Fractions from the Gels

The gel prepared at 0°C from 5% solution of 2 mL was dipped in water for 24 h and the dissoluted fractions were estimated by solvent evaporation.

Release of Brilliant Blue from the Gels

The gel containing Brilliant Blue was placed in a cubic wire net. The cube was hung on the predetermined position in the vial with buffer solution bath (400 mL) placed in the thermostat. The solution was stirred at 50 rpm to keep concentration constant. Five milliliters of the buffer solution was removed at a predetermined time after dip-

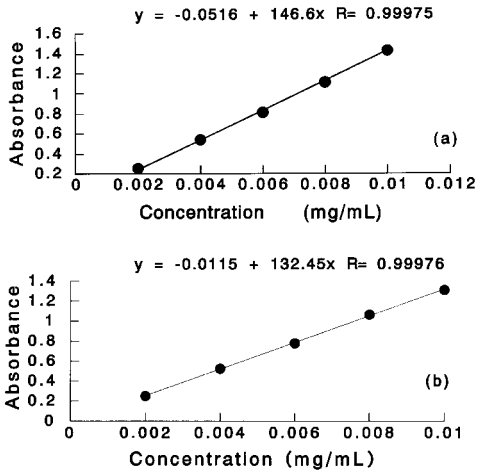

Figure 1 Working curves for Brilliant Blue in Buffer Solutions. (a): pH 4.0, (b): pH 7.4.

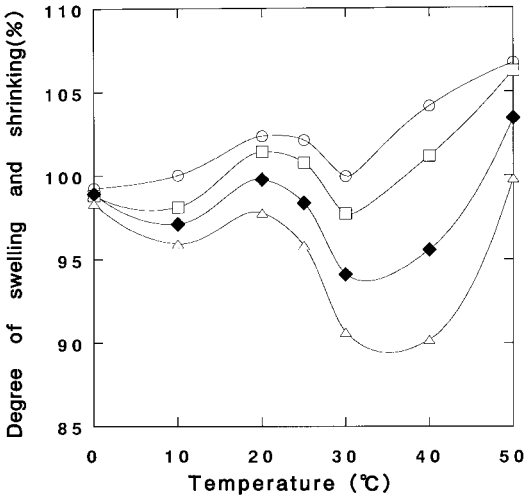

Figure 2 Swelling and shrinking behavior of 7.4-gel (*s*-PVA;10 wt %, pH 7.4, gelation at 0°C). ○: 12 h, □: 24 h, ◆: 36 h, △: 48 h.

ping the gel ($t = 0$), and a new buffer solution was added to the remaining solution to maintain the original volume. The concentration of Brilliant Blue of removed solutions were determined using the working curves of Brilliant Blue for corresponding pH by measuring the absorption at the wavelength of 629 nm.

Response of the Gels to the Repeating Changes of Temperature

The response test was studied by measuring the weight of gel. A gel was kept at 25°C. After 48 h the temperature was let down from 25°C to 0°C. Then the gel was kept at 0°C for 12 h. After that, it was kept at 25°C again. The temperature changes like this were performed twice.

Diffusion Exponent, *n*

The fractional release F ($F \leq 0.6$) follows the formula $F = M_t/M_\infty = kt^n$ (k = constant, n = diffusion exponent). The diffusion exponent n was estimated using this formula. Peppas et al. have reported that $n = 0.5$ was obtained in the analysis of the data in the first 15% of the fractional release from a cylindrical device, and $n = 0.45$ was obtained in the analysis of the data in the first 60% of it.[14–16] In this paper n was estimated using the data in the first 60% of it.

RESULTS AND DISCUSSION

Swelling Followed by Shrinking of the Gels

Figure 2 shows the swelling followed by contraction of the 7.4-gel prepared at 0°C with time at several temperatures. The solvent content of the gel kept at 0°C did not show any dramatic change, whereas for those of the gels kept at the temperatures above 0°C the gels were swollen in early stage, and then began to shrink, though no significant change of the degree of swelling at the temperature near 30°C were found. The swelling and shrinking is due to the breaking of smaller junctions and the dissolution of low-molecular-weight fractions, which was estimated to be 5–8% of the PVA used. The shrinking is due to the growth of larger junctions, respectively. The degree of shrinking had the maximum between 25°C and 40°C (48 h).

Effect of Release Temperature on Brilliant Blue Release from the Gel

Figure 3 shows the releases of brilliant blue from the 7.4-gel at different temperatures (27, 37, and 47°C at pH 7.4). The rate of release of Brilliant Blue increased with increasing temperature. All releases were completed within 12 h. As shown in Figure 2 the gels were at swelling stage within 12 h, and the degree of swelling increased with increasing temperature above 27°C. Table II shows the apparent diffusion exponents of the releases (27, 37, and 47°C at pH 7.4); they were 0.41–0.44, which were somewhat lower than 0.45 required for the cylindrical gel in the case of Fickian diffusion.[16–18] The degree of swelling of the gels prepared at 0°C is not on a stationary state in

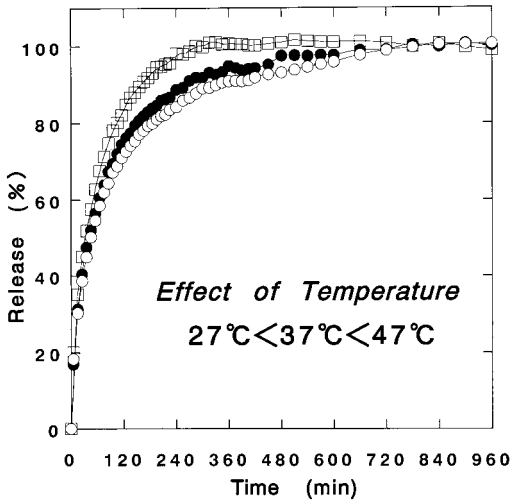

Figure 3 Effect of temperature on Brilliant Blue release from 7.4-gels (*s*-PVA; 10 wt %, pH 7.4, gelation at 0°C). ○: 27°C, ●: 37°C, □: 47°C.

Table II Diffusion Exponent (n) of Brilliant Blue

pH	4.0	7.4		
Temp (°C)	37	27	37	47
n	0.45	0.43	0.44	0.41

early stage of the release (Fig. 3) at the elevated temperatures. The *s*-PVA hydrogels begun to swell gradually when the gels was placed at higher temperatures (27, 37, and 47°C), therefore the diffusion from the gels was begun with swelling. Therefore, we submitted the release of Brilliant Blue from the *s*-PVA hydrogel at different temperatures is considered to be controlled by two factors: diffusion and swelling. The release was completed in 960 min in this gel. The gel for the prolonged release is considered to be prepared through the increase in the polymer concentration by solvent evaporation or with use of more syndiotacticity-rich PVA. The preparation is the future problem.

On-Off of Shrinking Behavior of the Gel

We studied whether the gel is available for thermally on-off switching device for drug release. Figure 4 shows the response of the 7.4-gel to repeating temperature changes between 0°C and 25°C. The poly(N-isopropylacrylamide-co-butylmethacrylate) gel showed reversible swelling characteristics,[14,15] whereas *s*-PVA gel did not show reversible swelling characteristics, but show thermosensitive on-off of shrinking behavior. The gel swelled at first step, and then began to shrink at next step at 25°C. When the temperature of the gel was let down from 25°C to 0°C and again raised to 25°C, the hydrogel swelled, and then began to shrink again. The on-off of shrinking of *s*-PVA hydrogel was observed when the process was performed twice using same sample. Figure 5 shows the effect of on-off of shrinking of the gels on the release. The rate of release at 5°C is lower than that at 27°C. This is considered to the shrinking of the holes between junctions. However, the cessation of the diffusion was not observed. No change of rate of release at 5°C was observed after one on-off cycle.

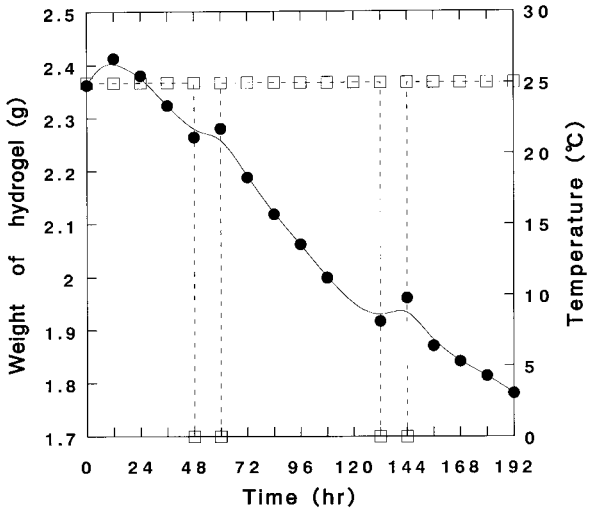

Figure 4 Response of *s*-PVA hydrogel to the repeating changes of temperature (*s*-PVA; 10 wt %, pH 7.4, gelation at 0°C). ●: Weight/g, □: Temperature/°C.

Swelling Followed by Shrinking of the Gels at Different pHs

Figure 6 shows swelling followed by shrinking of the 4.0-, 7.4-, and 9.0-gels at 37°C in the buffer solutions of pH 4.0, 7.4, and 9.0, respectively. The *s*-PVA hydrogel swelled at first stage and then shrank. The small junctions are broken at 37°C. The degree of swelling became large with the lowering of pHs. In the case of lower pH, the formation of intermolecular hydrogen bonds between PVA molecules is considered to be disturbed by H^+ ion to lead to make smaller junction. Therefore, the degree of swelling of *s*-PVA

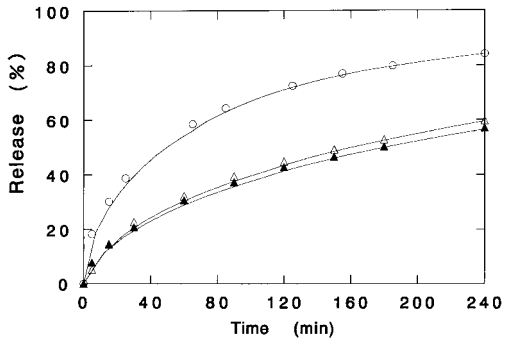

Figure 5 Effect of on-off of shrinking on release rate of Brilliant Blue from *s*-PVA hydrogels (*s*-PVA; 10 wt %, pH7.4). ○: 27°C, ▲: 5°C after preparation, △: 5°C after one on-off.

hydrogel on lower pH became large. On the other hand, the small quantity of small junctions is formed in the gel at higher pH.

Effect of pH on Brilliant Blue Release from the Gel

Figure 7 shows the release at different pHs (4.0 and 7.4). The release at pH 9.0 was not studied because the color of Brilliant Blue changes from blue to violet at the pH 9.0 to indicate the molecular structure change. As is expected from Figure 7, the rate of release of Brilliant Blue increased with decreasing pH. Table II shows the diffusion exponents of the release (37°C, pH = 4.0–7.4). The exponent for pH 4.0 was about 0.45 identical with the exponent for the cylindrical gel. The gels begun to swell immediately when the gels were placed at different pHs (pH = 4.0–9.0) as is shown in Figure 6. Therefore the diffusion from the gel is conducted in accordance with Fickian diffusion.

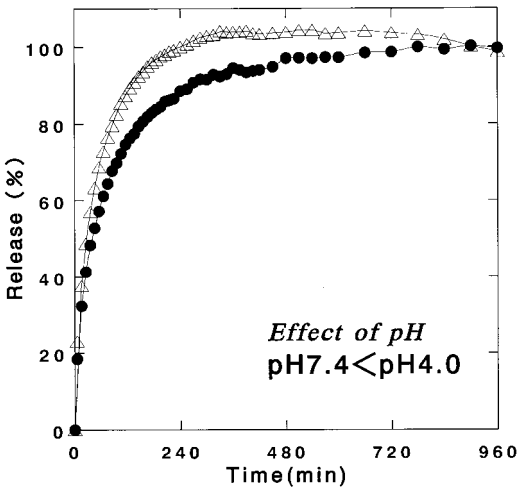

Figure 7 Effect of pH on Brilliant Blue release from *s*-PVA hydrogels (*s*-PVA;10 wt %, gelation at 0°C). △: pH 4.0, ●: pH 7.4.

CONCLUSIONS

When the *s*-PVA hydrogels prepared at 0°C with use of the buffer solution of pH 7.4 were placed in the buffer solution of elevated temperatures, the gels were swollen at first step, and then began to shrink at next step. The degree of swelling increased with dipping temperature except the temperatures near 30°C where no significant change was found. It also increased with decreasing pH between 4.0 and 9.0. The release of Brilliant Blue at 27, 37, and 47°C from the gel prepared at 0°C was dominated by two factors of diffusion and swelling. The apparent diffusion exponents of the release at pH 7.4 were 0.41–0.44 for the temperature range of 27–47°C corresponding to Fickian diffusion and swelling. The exponent at pH 4.0 (for 4.0 gel) was 0.45 corresponding to Fickian diffusion due to immediate swelling. The on-off of shrinking behavior of *s*-PVA hydrogels (7.4-gel) were observed under several temperature changes. The rate of release at 5°C was lower than that at 27°C and no change was observed at 5°C after one on-off cycle.

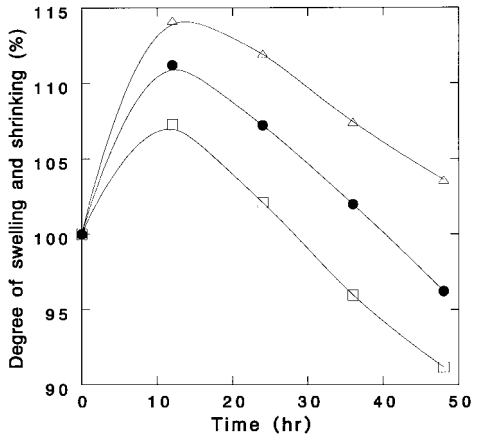

Figure 6 Swelling-shrinking behavior of *s*-PVA hydrogel under several pHs. △: pH 4.0, ●: pH 7.4, □: pH 9.0.

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