Application of Syndiotacticity-Rich PVA Hydrogels to Drug Delivery System

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SYNOPSIS

The preparation of stable syndiotacticity-rich poly(vinyl alcohol) (s-PVA) hydrogels is easier in comparison with that of the atactic poly(vinyl alcohol) (a-PVA) hydrogels. The drug release with use of s-PVA hydrogels containing indomethacin of 1.5 mg/mL buffer solution was studied under several conditions: at the gelation temperatures of 20–30°C, the release temperatures of 27–47°C, and pHs of phosphate buffer solutions of 6.6–7.4, for the gels with the concentrations of PVA of 3–8% using the degree of polymerization of 2170–4380. Indomethacin has been released spending 14 h. The diffusion exponents were 0.45–0.50, corresponding to Fickian diffusion. © 1995 John Wiley & Sons, Inc.

INTRODUCTION

Recently, many investigations have been carried out on the drug delivery system (DDS).[1-3] Among them are those with use of polymer gels.[4-14] The DDS, due to poly(vinyl alcohol) (PVA) hydrogels prepared from commercial PVA, has already been reported.[4-6,8-10,13,14] The gels were prepared by a freezing and thawing method in which the concentrations of PVA were usually over 10%. In the case of syndiotacticity-rich PVA (s-PVA), even if the concentration of PVA is lower than 5%, the stable hydrogels can be prepared at room temperature. That is, no freezing and thawing method is necessary for the preparation of s-PVA gels. In this article, the drug release from s-PVA hydrogels with different concentrations and thermal histories was studied at different temperatures (27–47°C) and pHs (6.0–7.4) with the use of s-PVA of different degrees of polymerization.

EXPERIMENTAL

Materials

The s-PVAs used are shown in Table I. All s-PVAs were prepared by sponification of poly vinyl trifiuoro acetates prepared by radical polymerization of vinyl trifluoroacetate at 60°C. Phosphate buffer solutions were prepared from phosphate buffer powder (Na_2HPO_4/KH_2PO_4). Phosphate buffer powder and indomethacin for biochemical material were purchased from Wako Pure Industries, Osaka, Japan.

Solubility Tests of Indomethacin

The solubility tests of indomethacin in phosphate buffer solutions were carried out in the usual way. The solubility of indomethacin at pH 6.6, 7.0, and 7.4 buffer solutions were 0.63 mg/mL, 3.07 mg/mL, and 3.46 mg/mL, respectively. The solubility test of indomethacin at pH 7.4 was carried out at 27°C, and the others were carried out at 37°C.

Working Curves of Buffer Solution

Each working curve for indomethacin in the buffer solution with a given pH was made by measuring absorbance at 271 nm using an ultraviolet-visible spectrophotometer (Shimazu Ultraviolet-Visible Spectrophotometer UV-160). The working curves obtained are shown in Figure 1.

Preparation of Cylindrical s-PVA Hydrogels Containing Indomethacin

The predetermined qualities of s-PVA, phosphate buffer solution, and indomethacin were added to test

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Table I Results of Polymerization

Sample	DP	s-Diad (%)		Triad (%) I	H	S
s-PVA-1	2170[a]	55.2[b]	57.4[c]	18.1[c]	49.0[c]	32.9[c]
s-PVA-2	4380[a]	55.8[b]	57.3[c]	18.2[c]	49.1[c]	32.7[c]

[a] From intrinsic viscosity of acetylated PVA using $[\eta] = 8.91 \times 10^{-3}DP^{0.62}$ (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.

tubes. After the s-PVAs were dissolved at 120°C, the tubes were opened and then stoppered with silicon plugs. The tubes were turned over to make cylindrical hydrogels. After that, the solutions were gelled at each gelation temperature for 24 h. In this matter the cylindrical hydrogels (diameter: 1.0 cm, length: 2.4 cm) were obtained.

Release of Indomethacin from s-PVA Hydrogel

The PVA hydrogel containing indomethacin was placed in a cubic wire net. The cube was hung on the predetermined position in the vial with phosphate buffer solution bath (400 mL) placed in a thermostat. The solution was stirred at 200 rpm to keep concentration constant. A part of the buffer solution was removed at a predetermined time after dipping the gel ($t = 0$), and a new buffer solution was added to the remaining solution to maintain the original volume. The concentration of indomethacin of the removed solutions were determined using the working curves of indomethacin by measuring the absorption at 271 nm.

Electron Micrographs of s-PVA Hydrogels with Different pHs

The electron micrographs of s-PVA hydrogels with different pHs (pH 6.6, 7.0, 7.4) were taken to observe the effect of pH on the structure of hydrogels using a scanning electron microscope (JEOL JSM-T220A). The gels prepared in the way described above were placed in phosphate buffer solution at 37°C for 14 h. Before observation, hydrogels were frozen and dried under cooling to prevent the contraction of the gels as much as possible.

RESULTS AND DISCUSSION

Effect of Gelation Temperature on Drug Release from s-PVA Hydrogel

Figure 2 shows the effect of gelation temperature on indomethacin release. At the early time, the rate of release decreased with increasing gelation temperature. The final release amounts of indomethacin were about 60% at 20°C, and 50% at 25–30°C, respectively; the amount of drug release at 20°C was larger than that at the other temperature. The relationship between the gelation temperature and the heat of fusion of gel junctions (ΔH) have already been investigated.[15] ΔH of 20°C gel is highest among 20, 25, and 30°C gels, and ΔH of 20, 25, and 30°C gel decreases in that order. Therefore, the size of

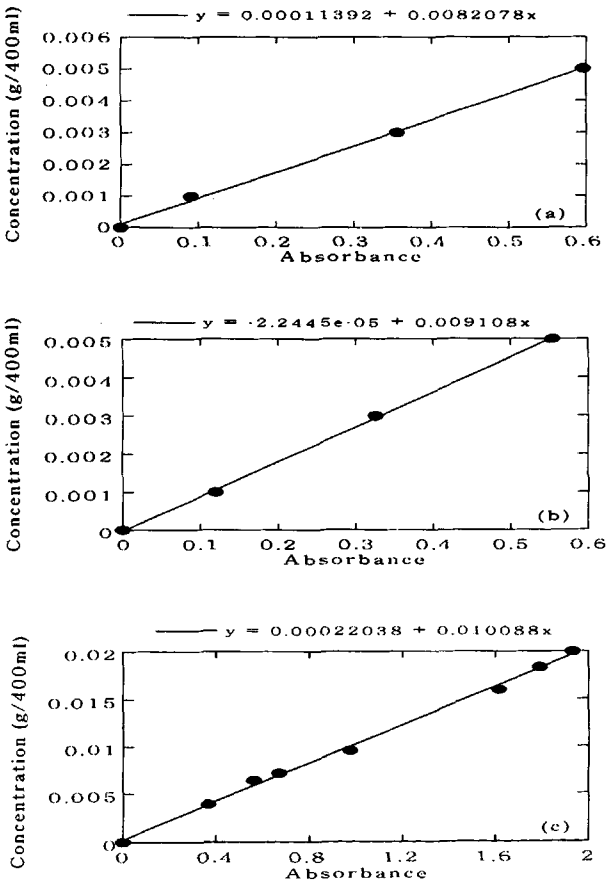

Figure 1 Working curves of buffer solutions (271 nm): (a) pH 6.6, (b) pH 7.0, (c) pH 7.4.

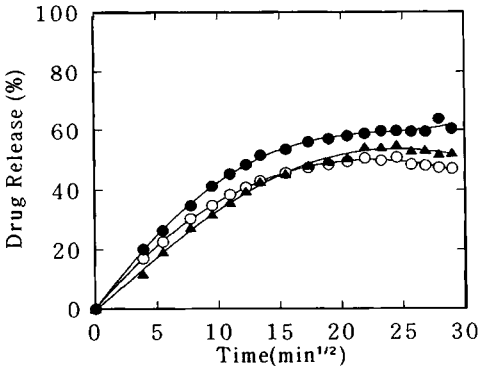

Figure 2 Effect of gelation temperature on indomethacin release from s-PVA hydrogels (s-PVA-1, 5% PVA, pH 7.4, release at 37°C): ● 20°C, ○ 25°C, ▲ 30°C.

junctions of 20°C gel is largest among these three gels. The fraction of crystallites for the 20°C gel is largest. This leads to a decrease of the dissolved segment concentration and an increase in the diffusion of indomethacin. To keep gelation temperature constant is essential for the realization of both the homogeneous crystallization of gels and the stable release of indomethacin.

Effect of Release Temperature on Drug Release from s-PVA Hydrogel

Figure 3 shows the indomethacin release at 27, 37, and 47°C for gels prepared at 30°C. The difference in the rate of release between at 27°C and at 37°C was small, and the rate of release at 47°C was larger than the others. ΔH at 27, 37°C are about 100 kJ/mol, whereas ΔH at 47°C is 180–190 kJ/mol.[15] When the gel, prepared at 30°C, is heated to 47°C, the junctions grow leading to the large difference. Figure 4 shows the time course of transmittance of gels

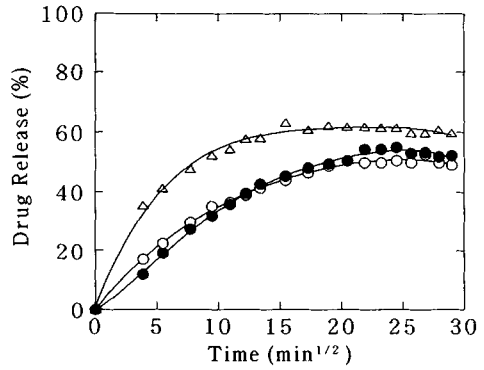

Figure 3 Effect of temperature on indomethacin release from s-PVA hydrogels (s-PVA-1, 5% PVA, pH 7.4, gelation at 30°C): ○ 27°C, ● 37°C, △ 47°C.

that were gelled at 30°C for 24 h and then changed to the indicated temperature. On the whole, with increasing release temperature, the drop of transemittance becomes large. As expected, when the gel prepared at a temperatures is changed to a different temperature, the structure of the gel is changed, leading to the difference on the release.

Effect of pH on Drug Release from s-PVA Hydrogel

Figure 5 shows the effect of pH on drug release. The rate of release increased with decreasing pH. At pH = 6.6, indomethacin was released completely after 14 h, whereas at pH 7.4 and 7.0, about 60% of it was released. Figure 6 shows the time courses of transmittance of gels of which pHs were 6.6, 7.0, and 7.4. The drop of transmittance became large with increasing pH. The formation of interchain hydrogen bonds in the gels is accelerated by OH ions in buffer

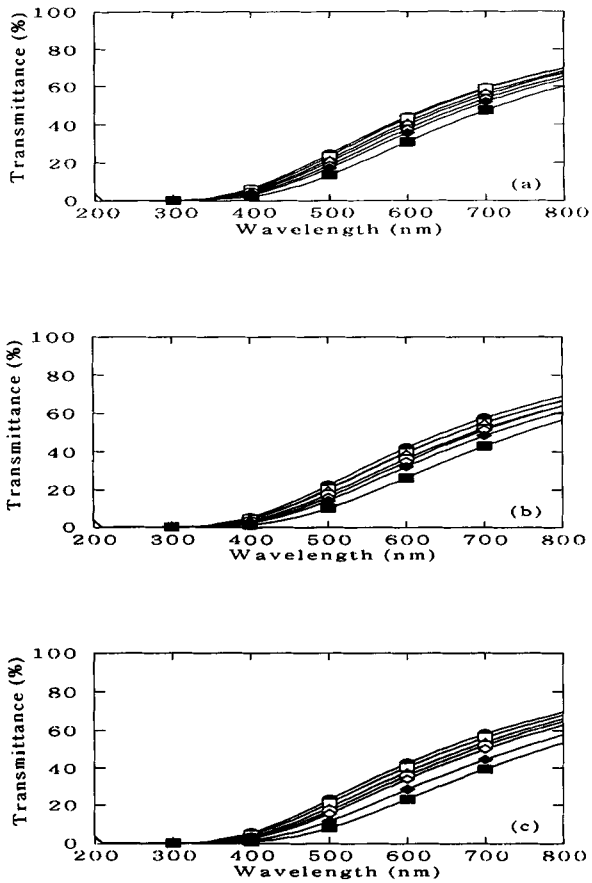

Figure 4 Change of transmittance (s-PVA-1, 5% PVA, pH 7.4, gelation at 30°C): (a) at 27°C, (b) at 37°C, (c) at 47°C. Standing time: ● 25/min, □ 100/min, △ 225/min, ○ 400/min, ◇ 625/min, ♦ 900/min, ■ 1880/min.

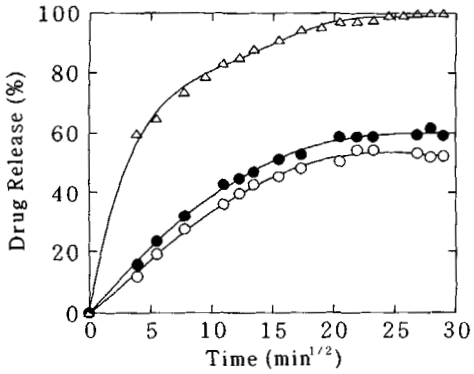

Figure 5 Effect of pH on indomethacin release from s-PVA hydrogel (s-PVA-1, 5% PVA, release at 37°C, gelation at 30°C): △ pH 6.6, ● pH 7.0, ○ pH 7.4.

solutions during the release at pH = 7.0 and pH = 7.4. Therefore, the release of indomethacin from gels is suppressed. On the other hand, because of the inhibition of the formation of interchain hydrogen bonds in the gels at pH = 6.6, the distance be-

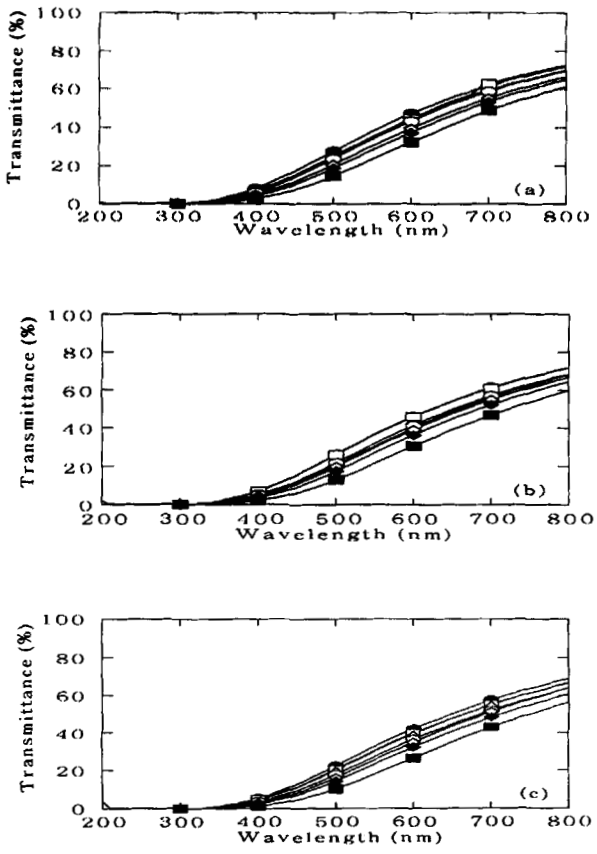

Figure 6 Change of transmittance at 37°C (s-PVA-1, 5% PVA, gelation at 30°C): (a) pH 6.6, (b) pH 7.0, (c) pH 7.4. Standing time: ● 25/min, □ 100/min, △ 225/min, ○ 400/min, ◇ 625/min, ◆ 900/min, ■ 1880/min.

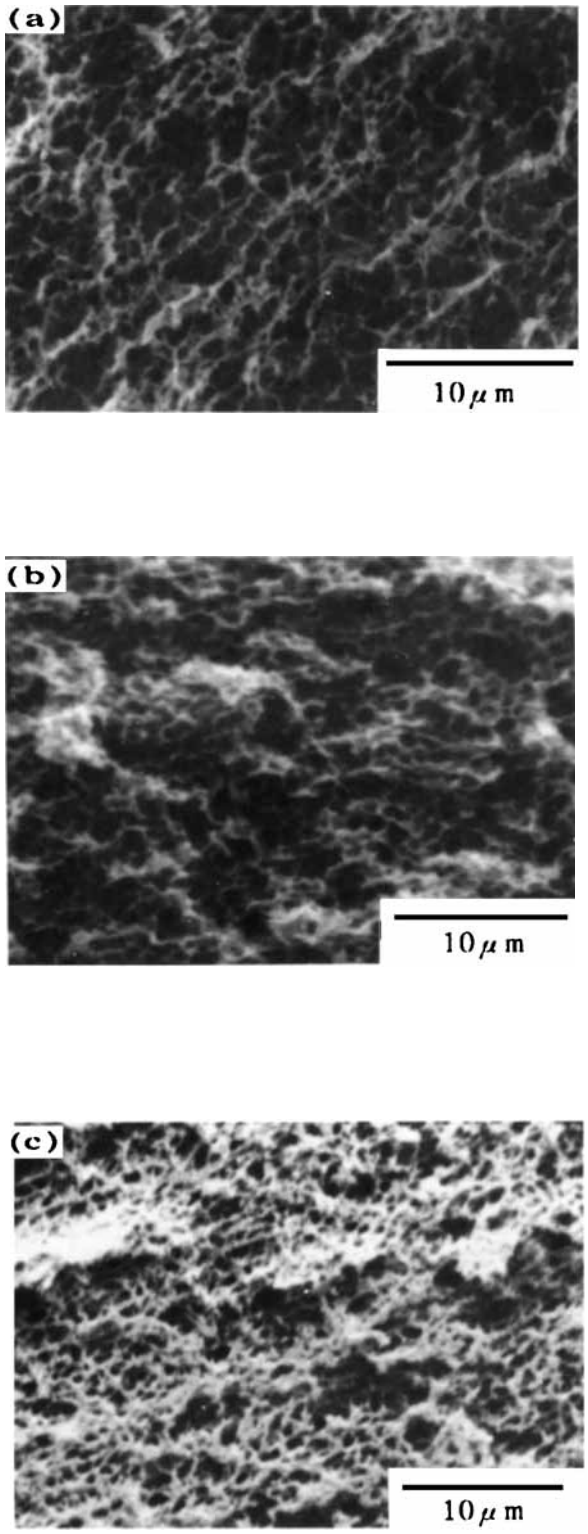

Figure 7 Electron micrographs of s-PVA hydrogels (s-PVA-1, 5% PVA, gelation at 30°C): (a) pH 6.6, (b) pH 7.0, (c) pH 7.4.

tween molecules becomes larger, leading to easier passage of indomethacin through the intermolecular space. Therefore, both the rate and the final quantities of the release from gels were increased. Figure 7 shows the electron micrographs of s-PVA hydrogels with different pHs (pH 6.6, 7.0, and 7.4). Every gel had a network structure. The average of the hole diameter for pH 6.6, 7.0, and 7.4 was about 0.94 μm, 0.68 μm and 0.48 μm, respectively. It depends remarkably on pH. Ikada et al. have reported that the rate of drug release became larger with increasing pH.[9] They attributed this to the rate of dissolution of indomethacin. The PVA used in the study was atactic PVA (a-PVA). The structure of a-PVA hydrogels is different with that of s-PVA hydrogels in which holes are considerably smaller.[4] Therefore, the effect of gel structure corresponding to pH on the release was not observed.

Effect of Degree of Polymerization (DP) on Drug Release from s-PVA Hydrogel

Figure 8 shows the effect of DP on drug release. At an early stage, the difference in the rate of release was hardly discernible, but the final quantity of release from the gel of the polymers with DP of 4380 was about 40%, whereas that for the gel of the polymers with DP of 2170 was 60%. Figure 9 shows the effect of DP on the time course of transmittance of gels. The drop of transmittance of the gel of the polymer with DP of 4380 with time was smaller than that of the gel of the polymer with DP with 2170. It seems that the junctions in the gel prepared with the polymer with DP of 2170 grow more easily during release in comparison to that with the polymer with DP of 4380. The easier growth makes the concentration of segments in the swollen regions in the former gel lower, leading to the easier diffusion of indomethacin in the former gel. Therefore, the final quantity of release from the gel of the polymers with DP of 4380 decreased.

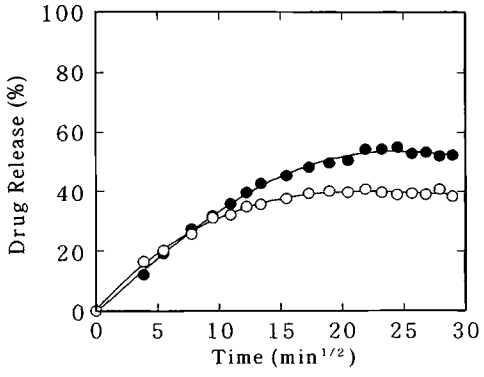

Figure 8 Effect of degree of polymerization on indomethacin release from s-PVA hydrogels (5% PVA, release at 37°C, pH 7.4, gelation at 30°C): ● DP = 2170, ○ DP = 4380.

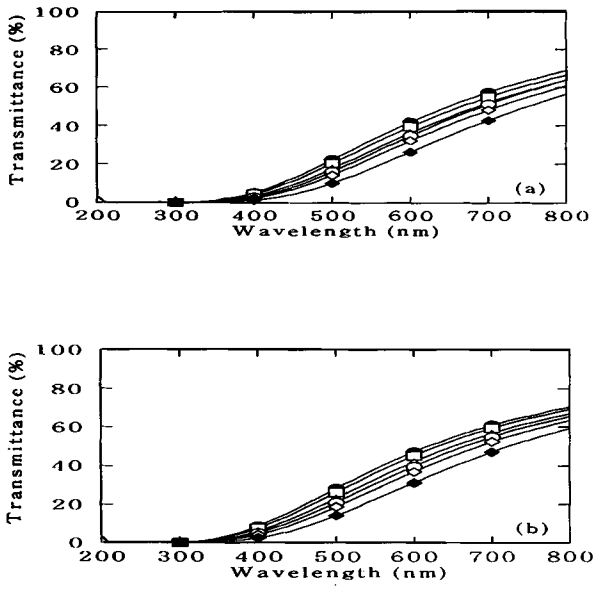

Figure 9 Change of transmittance at 37°C (5% PVA, gelation at 30°C, pH 7.4): (a) DP = 2170, (b) DP = 4380. Standing time: ● 25/min, □ 100/min, △ 225/min, ○ 400/min, ◇ 625/min, ◐ 900/min, ■ 1880/min.

Effect of Concentration of PVA on Drug Release from s-PVA Hydrogel

Figure 10 shows the effect of concentration of PVA on drug release. On the whole, both the rate and the final quantities of the release increased with increasing concentration of PVA. The concentration of indomethacin in the swollen region in hydrogels

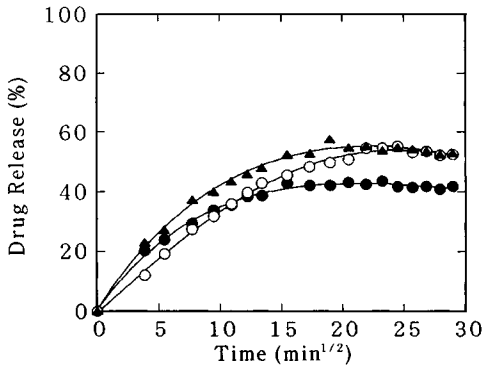

Figure 10 Effect of concentration of PVA on indomethacin release from s-PVA hydrogels (s-PVA-1, release at 37°C, gelation at 30°C, pH 7.4): ● 3%, ○ 5%, ▲ 8%.

increases with increasing concentration of PVA. Therefore, the concentration gradient in the outer part of the gel increased. The reasons for the large initial rate of release at 3% are due to lower concentration. This makes indomethacin easily to pass thought the intermolecular regions.

Diffusion Exponent, *n*

The fractional release F ($F \leqq 0.6$) followed the formula $F = M_t/M_\infty = kt^n$ (k: constant, n: diffusion exponent). Table II shows the diffusion exponent n estimated in the formula. N. A. 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. Because all values were in the vicinity of 0.45–0.50, these releases were regarded as Fickian diffusion.[5,6]

CONCLUSIONS

The drug release from s-PVA hydrogels has been studied with use of indomethacin of 1.5 mg/mL buffer solution under several conditions. The rate of release decreased with increasing gelation temperature at the early stage. The final release amounts of indomethacin for 20°C gel was larger than that for 25 and 30°C gels. Both the rate of release and the final release amounts of indomethacin increased with increasing release temperature in the temperature range between 27 and 47°C. The rate of release increased with decreasing pH. At pH = 6.6, indomethacin was released completely after 14 h, whereas at pH 7.4 and 7.0, about 60% of it was released. In the early stages, the difference in the rate of release was hardly discernible between the gels with two kinds of s-PVAs (degree of polymerization of 2170 and 4380), but the final quantity of release from the gel of the degree of polymerization of 4380 was about 40%, which was smaller than that of DP = 2170 (52%). Both the rate and the final quantities of release increased with increasing concentration of PVA.

Indomethacin release stopped after about 14 h. The diffusion exponents were 0.45–0.50, corresponding to Fickian diffusion.

Table II Diffusional Exponent, *n* for Each Experiment

Experimental Conditions[a]				
DP of PVA	Conc. of PVA (%)	pH of PBS	Release Temp. (°C)	*n*
			27	0.48
2170	5	7.4	37	0.50
			47	0.41
		6.6		0.44
2170	5	7.0	37	0.53
		7.4		0.50
2170	5	7.4	37	0.50
4380				0.45
	3			0.43
2170	5	7.4	37	0.50
	8			0.44

[a] Gelation temp. at 30°C.

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