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Report

Evaluation of Polyvinyl Alcohol Hydrogel as a Sustained-Release Vehicle for Rectal Administration of Indomethacin

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In order to evaluate an indomethacin polyvinyl alcohol (PVA) hydrogel for rectal administration, the *in vitro* release characteristics of indomethacin from the hydrogel and indomethacin plasma concentrations after rectal administration were examined. The PVA hydrogel containing indomethacin was prepared by a low-temperature crystallization method. The release of indomethacin from the PVA hydrogel agreed with the Fickian diffusion model for 10 hr. Rectal administration of indomethacin hydrogels to rats yielded high indomethacin plasma concentrations, without producing a sharp peak, and a sustained-release effect. In dogs, the indomethacin hydrogel produced a similar sustained-release effect; however, the indomethacin plasma concentration was relatively low compared with that of an indomethacin suppository.

KEY WORDS: hydrogel; polyvinyl alcohol; rectal administration; indomethacin.

INTRODUCTION

A hydrogel is defined as a hydrophilic polymer which swells in water, retaining significant amounts of water within its structure but remaining water insoluble (1). Hydrogels of hydroxyethyl methacrylate (HEMA) have been used for controlled-release drug delivery systems (1–3). Recently, Leed *et al.* reported that hydrogels of HEMA cross-linked with ethyleneglycol dimethacrylate (EGDMA) have potential as a flexible rectal drug delivery system (4). Hyon and Ikada also reported that a novel polyvinyl alcohol (PVA) hydrogel, prepared by a low-temperature crystallization method, was useful as a transdermal therapeutic system (5). The PVA hydrogel has a porous, three-dimensional network structure with a high mechanical strength and high water content.

Indomethacin is used extensively in the therapy of inflammatory diseases. In order to prevent morning pain and stiffness when dosing indomethacin before bedtime, it may be necessary to maintain a suitable concentration of indomethacin in plasma for at least 10 hr.

In the present study, PVA hydrogel, a fully swollen hydrogel, was used as a controlled-release delivery system for rectal administration of indomethacin. In order to evaluate the hydrogel preparation, the *in vitro* release characteristics of indomethacin from hydrogels and the indomethacin plasma profile after rectal administration were examined.

MATERIALS AND METHODS

Materials

PVA (degree of saponification, 99.5 mol%, mean degree of polymerization, 1700) was obtained from Unichika Ltd. (Osaka, Japan), and indomethacin from Sigma Chemical Inc. (St. Louis, Mo.). All other chemicals were of reagent grade and were obtained commercially.

Preparation

Hydrogel containing indomethacin was prepared using the low-temperature crystallization method described by Hyon and Ikada (5). Briefly, PVA was dissolved in 1/15 *M* phosphate buffer (pH 6.4, 7.4, and 8.6) at about 80°C to give concentrations of 8, 10, 15, 20, and 25% (w/v). Then indomethacin was added to the PVA solutions at room temperature, with the final pH of these solutions being 6.2, 7.0, and 8.0. The PVA solutions containing indomethacin were poured into plastic syringes (4.5 mm × 1.2 cm) for rectal administration in rats and into plastic molds (7.0 mm × 1.8 cm) for rectal suppository (Kanae Co., Osaka, Japan; 1-ml vol) for rectal administration in dogs and release tests. The hydrogels containing indomethacin were formed by freezing the mixtures at −10°C for 15 hr to allow crystallization of PVA, followed by thawing at 4–5°C for 24 hr. The hydrogel preparations were stored at room temperature and were used

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within 2 weeks except for the pH 8.0 preparation, which was used within 2 days. For comparative study, indomethacin suppositories were prepared with Witepsol H-15 (Dynamit Nobel, Witten, West Germany) using the fusion method.

Release Tests

The release rate of indomethacin from the hydrogel was investigated by the JP XI paddle method. The dissolution fluid (400 ml) was 1/15 *M* phosphate buffer (pH 7.4) maintained at 37°C. The hydrogel was held at the bottom of the vessel in stainless-steel wire mesh (sinker). The paddle was positioned approximately 2.5 cm from the bottom of the vessel and was rotated at 50 rpm. Two milliliters of each sample was removed at predetermined times, and 2 ml of fresh fluid was added to the vessel to maintain the original volume. The concentration of indomethacin was assayed spectrophotometorically at 266 nm. Release-rate data were analyzed on the basis of physical models (Fickian and Non-Fickian drug release model) (6).

Rectal Administration

Administration in Rats. Wistar-strain male rats, weighing 190 to 230 g, were fasted for 17 hr prior to the experiments. Following pentobarbital-Na (50 mg/kg) anesthesia, the dosage of the hydrogel preparation was 0.95 g/kg and the dose of indomethacin was 20 mg/kg. For comparison, rectal administration of the indomethacin suppository (Witepsol H-15) was also performed. Blood samples (0.5 ml) were collected from the inguinal vein at 15 and 30 min and 1, 3, 5, 7, 9, and 24 hr after administration.

Administration in Dogs. Four beagle male dogs, weighing 9.5 to 12 kg, were fasted 24 hr prior to the experiments. The indomethacin hydrogel was administered into the rectum without anesthesia. The dosage of the hydrogel preparation was 0.95 g/dog and the dose of indomethacin was 20 mg/dog. Blood samples (2.5 ml) were collected from the foreleg vein at 30 min and 1, 3, 5, 7, and 9 hr after administration.

Assay Procedure. The plasma samples were obtained by centrifugation of heparinized blood samples. The quantity of indomethacin was determined by the high-performance liquid chromatographic (HPLC) method described by Yaginuma *et al.* (7).

RESULTS

Release Tests

Release-rate data from swelling polymeric hydrogels can generally be treated by using simple empirical equations (6). Phenomenologically it is possible to express the fractional release F as a function of time t for at least the early time period ($F \leq 0.06$): $F = M_t/M_\infty = k \cdot t^n$, where k is a constant characteristic of the hydrogel system and n is indicative of the type of transport mechanism. The situation of $n = 1$ corresponds to zero-order release kinetics, $1 > n > 0.5$ corresponds to the non-Fickian diffusion model, and $n = 0.5$ corresponds to the Fickian diffusion model (Higuchi model) (6,8). The kinetic parameters for indomethacin released from hydrogel preparations are shown in Table I. The derived n values, obtained by using values of $F \leq 0.6$, approached 0.5. Therefore, the indomethacin release from hydrogel preparations followed the Fickian diffusion model.

The effects of the PVA concentration and the pH of the hydrogel preparations were plotted as the percentage release against the square root of time (Figs. 1 and 2). Slower release of indomethacin occurred at the higher PVA concentration (Fig. 1). On the other hand, indomethacin release decreased with lower pH levels (Fig. 2).

Rectal Administration

Figure 3 shows the indomethacin plasma concentrations following administration of indomethacin as a hydrogel (pH 7.0) at various PVA concentrations and as a suppository (Witepsol H-15) to rats. Rectal administration of the indomethacin suppository caused an early peak in the plasma level and a high maximum concentration. Then indomethacin was eliminated rapidly from plasma. On the other hand, the indomethacin plasma concentrations after rectal administration of indomethacin hydrogels were relatively low at early times and showed a sustained plateau level compared with the suppository. The indomethacin plasma concentration profiles were similar for the 10, 15, and 20% (w/v) PVA hydrogels up to 9 hr after rectal administration. The trend of the plasma concentrations at 24 hr is consistent with that expected from the *in vitro* data, i.e., increased duration with increasing PVA content. Further, the indomethacin plasma concentrations with 15 and 20% (w/v) PVA hydrogels remained constant over 24 hr after administration.

Figure 4 shows the indomethacin plasma concentrations when indomethacin hydrogels [10% (w/v) PVA] of various pH levels were administered rectally to rats. Higher plasma concentrations of indomethacin were obtained at higher pH levels. The indomethacin plasma concentration with the pH 8.0 hydrogel preparation was particularly high. The mean $AUC_0^{9\ hr}$ values ($\pm$SE; $N = 4$) after rectal administration of hydrogel preparations [10% (w/v) PVA: pH 7.0 and pH 8.0,

Table I. Kinetic Parameters for Indomethacin Release from Hydrogel Preparations

Indomethacin hydrogel preparation	M_t/M_∞	Release exponent n	Kinetic constant k (% · min^{-n})	Correlation coefficient r
8% PVA (pH 7.0)	0.6	0.500	3.155	0.998
10% PVA (pH 7.0)	0.6	0.528	2.500	0.998
15% PVA (pH 7.0)	0.6	0.537	2.094	0.999
20% PVA (pH 7.0)	0.6	0.535	1.945	0.999
25% PVA (pH 7.0)	0.6	0.536	1.845	0.999
10% PVA (pH 6.2)	0.6	0.537	2.099	0.999
10% PVA (pH 8.0)	0.6	0.526	3.327	0.999

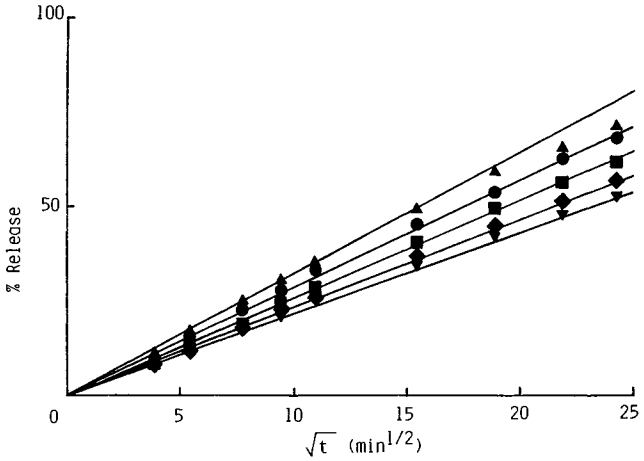

Fig. 1. Release profiles of indomethacin from PVA hydrogel preparations (pH 7.0) at various PVA concentrations. Concentrations of PVA (w/v): 8% (▲); 10% (●); 15% (■); 20% (♦); 25% (▼).

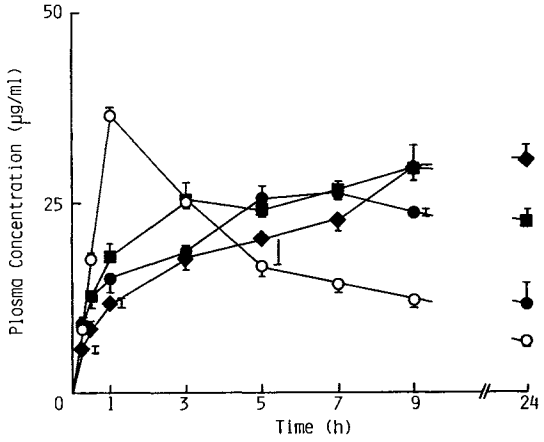

Fig. 3. Plasma concentrations of indomethacin following rectal administration of PVA hydrogel preparations (pH 7.0) at various PVA concentrations in rats. Concentrations of PVA (w/v): 10% (●); 15% (■); 20% (♦). Witepsol H-15 (○). Dose of indomethacin was 20 mg/kg body weight. Each value represents the mean ± SE of four rats.

190.66 ± 8.86 and 340 ± 27.89 μg · h/ml, respectively] were larger than that of the indomethacin suppository (179.68 ± 8.76 μg/ml) in rats.

Figure 5 shows the indomethacin plasma concentrations when indomethacin hydrogels [10 and 15% (w/v) PVA, pH 7.0] and the indomethacin suppository (Witepsol H-15) were administered rectally to dogs. The indomethacin plasma concentrations obtained with the indomethacin hydrogels were relatively low. However, sustained plateau levels were found over longer times compared with that of the indomethacin suppository. The mean $AUC_0^{9\ hr}$ values (±SE; N = 4) after rectal administration of the hydrogel preparations (10% PVA, pH 7.0, 3.88 ± 0.48 μg · h/ml) were slightly lower than that of the indomethacin suppository (5.67 ± 1.0 μg/ml) in dogs.

DISCUSSION

Drug release from hydrogels depends on the nature of hydrogel used, particularly the degree of cross-linking, the size of water channels, and the drug equilibrium between the polymer and the external water phase (9). Kim described that the plots of drug release [$v \cdot (t)^{1/2}$] from hydrogels were two straight lines with a breaking point due to change in characteristics during water absorption by the hydrogel device (1). In this *in vitro* release experiment, the profiles of indomethacin release from hydrogel preparations showed only a straight line for the cumulative amount of released indomethacin versus the square root of time. Thus, drug release followed the Fickian diffusion model (6). This result may be caused by the porous and three-dimensional network structure of PVA hydrogels with a high mechanical strength and high water content. Furthermore, PVA hydrogel is a nonerodible and insoluble matrix (5).

The release rates of indomethacin from hydrogel preparations were affected by the PVA concentration and the pH. Higher concentrations of PVA resulted in a higher network system and lower drug release rates. On the other

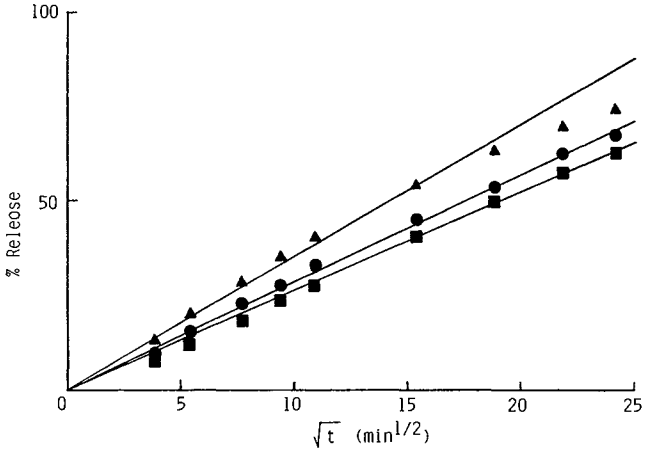

Fig. 2. Release profiles of indomethacin from PVA hydrogel preparations [10% (w/v) PVA] at various pH levels of PVA hydrogels: pH 6.2 (■); pH 7.0 (●); pH 8.0 (▲).

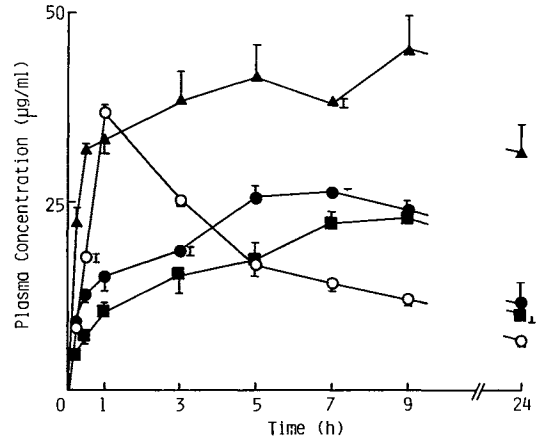

Fig. 4. Plasma concentrations of indomethacin following rectal administration of PVA hydrogel preparations [10% (w/v) PVA] at various pH levels in rats. pH of PVA hydrogels: pH 6.2 (■); pH 7.0 (●); pH 8.0 (▲). Witepsol H-15 (○). Dose of indomethacin was 20 mg/kg body weight. Each value represents the mean ± SE of four rats.

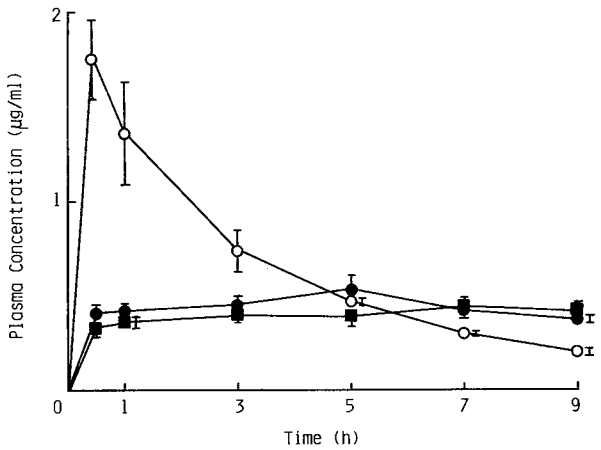

Fig. 5. Plasma concentrations of indomethacin following rectal administration of PVA hydrogel preparations (pH 7.0) at various PVA concentrations in dogs. Concentrations of PVA (w/v): 10% (●); 15% (■). Witepsol H-15 (○). Dose of indomethacin was 20 mg/dogs. Each value represents the mean ± SE of four dogs.

hand, higher pH levels of hydrogels showed higher release rates. Indomethacin, an acidic (pK_a = 4.5) and poorly water-soluble drug, is saturated in the external water phase of hydrogels. Solubilities of indomethacin were 0.26, 0.72, and 1.42 mg/ml in pH 6.2, 7.0, and 8.0 buffer solutions, respectively. Thus, different pH values could lead to different dissolution rates, accounting for the observed differences in drug release rate.

In the *in vivo* absorption experiment in rats, the indomethacin hydrogel preparation gave plateau plasma levels of the drug after rectal administration without producing a sharp plasma concentration peak. The pH of the hydrogel preparations affected the rectal absorption rates of indomethacin. A higher pH of the indomethacin hydrogel resulted in a higher plasma concentration of indomethacin, as expected from the *in vitro* release experiments. On the other hand, the concentration of PVA in the hydrogel preparations did not affect the indomethacin plasma profiles for up to 9 hr after rectal administration. However, the indomethacin plasma concentrations tended to be increased with increasing PVA content at 24 hr. This persistence of indomethacin plasma concentrations is consistent with the results of the *in vitro* release experiment.

The rectal administration of indomethacin hydrogel preparations in dogs also induced a plateau plasma level of the drug without producing a sharp peak of plasma concentration. However, the indomethacin plasma concentrations were relatively low. The bioavailability of the indomethacin hydrogel, relative to the suppository, was approximately 70% in dogs. The lower bioavailability may be determined by the relative contact area of the hydrogel preparation to the rectal mucosal surface, which is smaller in the dog than in the rat. Further, the hydrogel preparation cannot readily spread in the rectal lumen compared to a conventional suppository.

In conclusion, indomethacin PVA hydrogels may be useful as a rectal preparation with reduced side effects and with prolonged action.

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