

Design of Polyvinyl Alcohol Hydrogel as a Controlled-Release Vehicle for Rectal Administration of *dl*-Propranolol-HCl and Atenolol

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Preparations of beta-blockers, propranolol-HCl and atenolol, in poly(vinyl alcohol) (PVA) hydrogel were designed for the therapeutic treatment of hypertension by transrectal delivery. *In vitro* release characteristics and plasma drug concentration profiles after rectal administration in rats and dogs were examined. The PVA hydrogels containing β -blockers were prepared by a low-temperature crystallization method. The release of β -blockers from hydrogel preparations was consistent with Fickian diffusion (Higuchi model); the drug release versus the square root of release time profile gave a straight line over 60% of the total release process. The release of β -blockers from hydrogel preparations increased at higher concentrations of PVA in the hydrogel preparations and was not affected by the pH of hydrogel preparations. Plasma concentrations of β -blockers after rectal administration of hydrogels were higher than those after administration of suppositories (Witepsol H-15) in rats and dogs. The drug plasma concentrations increased at higher concentrations of PVA in hydrogel preparations. In the case of propranolol, which is a hepatic high-clearance drug, area under the blood concentration curve, 0–8 h after rectal administration of a hydrogel preparation (20% w/w PVA, pH 7.0) was 2.16 times and 5.26 times higher than those obtained with Witepsol H-15 suppository and oral administration, respectively. Rectal administration with PVA hydrogels is a favorable route for a hepatic high-clearance drug such as propranolol.

Keywords polyvinyl alcohol; hydrogel; β -blocker; propranolol; atenolol; rectal administration; absorption; controlled release

Introduction

Beta-adrenergic blocking agents (β -blockers) now occupy an important place in the treatment of angina pectoris, hypertension and other cardiovascular diseases. However, the bioavailability of oral dosage forms of some β -blockers such as propranolol is low and varies from individual to individual.¹⁾ These problems have been attributed to extensive drug metabolism during absorption and first passage through the liver. Rectal administration may be useful for drugs that are subject to after oral administration due to first-pass metabolism.²⁾

Recently, the hydrogel system has been receiving considerable attention as a device for drug delivery. Poly(vinyl alcohol) (PVA) hydrogel, prepared by the low-temperature crystallization method, has a porous and three-dimensional network structure with high mechanical strength and a high water content.^{3,4)} We have previously reported the rectal administration of indomethacin, a non-steroidal anti-inflammatory drug,³⁾ and the transdermal delivery of bunitrolol-HCl, a β -blocker,⁴⁾ using PVA hydrogels; an improved therapeutic effect with prolonged action was obtained.

In the present study, PVA hydrogel, a fully swollen hydrogel, was used for the controlled rectal administration of β -blockers, propranolol-HCl and atenolol. Propranolol represents a model hepatic high-clearance drug and atenolol, a model hepatic nonclearance model drug.¹⁾ In order to evaluate the hydrogel preparations the following points were investigated; i) the *in vitro* release characteristics of β -blockers from PVA hydrogels and ii) plasma concentrations of β -blockers after rectal administration in rats and dogs.

Materials and Methods

Materials PVA (degree of saponification; 99.5 mol%, mean degree of polymerization; 1700) was obtained from Unichica Ltd. (Osaka, Japan), and *dl*-propranolol-HCl and atenolol from Sigma Chemical Inc. (St. Louis, Mo. U.S.A.). All other chemicals were of reagent grade and were

obtained commercially.

Preparations Hydrogels containing β -blockers were prepared using the low-temperature crystallization method described in our previous papers.^{3,4)} Briefly, PVA was dissolved in 1/15 M phosphate buffer (pH 6.5, 7.0 and 8.0) for propranolol-HCl and 1/5 M phosphate-1/10 M citrate buffer (pH 5.3, 6.0 and 6.6) for atenolol at about 90°C to give concentrations of 10, 15 and 20% w/w. Then β -blockers were dissolved in PVA solutions at room temperature with final pH solutions being 6.5, 7.0 and 8.0. The PVA solutions containing β -blockers were poured into plastic syringes (4.5 mm i.d. \times 1.8 cm) for rectal administration in rats and into plastic suppository mold (7.0 mm i.d. \times 1.8 cm; 1 g preparation and 10.0 mm \times 3.0 cm; 2 g preparation, Kanoe Co., Osaka, Japan) for rectal administration in dogs and release tests. The hydrogels containing β -blockers were formed by freezing the mixtures at -20°C for 15 h to allow crystallization of PVA, followed by thawing at 5°C for 24 h. The hydrogel preparations were stored to inhibit aqueous evaporation at room temperature and were used within 2 weeks. In a comparative study, β -blocker suppositories were prepared with Witepsol H-15 (Dynamit Nobel, Witten, West Germany) using the fusion method and β -blockers were dissolved in isotonic buffer (pH 7.4) for oral administration.

Release Tests The release rate of β -blocker from the hydrogel (1 g) 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 preparation was held at the bottom of the vessel in a 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. An aliquot (2 ml) of dissolution fluid was removed at predetermined times and 2 ml of fresh fluid was added to the vessel to maintain the original volume. The concentrations of propranolol and atenolol were assayed spectrophotometrically at 291 and 225 nm, respectively. Release-rate data were analyzed on the basis of physical models (Fickian and non-Fickian drug release models).⁵⁾

Rectal Administrations in Rats and Dogs Wistar strain male rats, weighing 260 to 320 g, were fasted for 17 h prior to the experiments. Following pentobarbital-Na (50 mg/kg) anesthesia, hydrogel preparations were administered into the rectum (2 cm section above the anus). The dosage of the hydrogel preparation was 1.0 g/kg and the doses of propranolol-HCl and atenolol were 10 and 20 mg/kg, respectively. For comparison, rectal administration of β -blocker suppositories (Witepsol H-15) was also carried out. Blood samples (0.5 ml) were collected from the inguinal vein at 30 min and 1, 2, 4, 6, 8 and 10 h after administration.

Four beagle male dogs, weighing 9.5 to 13 kg, were fasted for 24 h prior to the experiments. The β -blocker hydrogel preparations were administered into the rectum without anesthesia. The dosage of hydrogel preparation was 1 or 2 g/dog and the dose of β -blockers was 100 mg/dog. Blood

samples (2.5 ml) were collected from the foreleg vein at 30 min and 1, 3, 5, 7, and 9 h after administration. In other rats under pentobarbital anesthesia, the change in arterial blood pressure was directly measured with a pressure transducer after rectal administration. Assay procedure. The plasma samples were obtained by centrifugation of heparinized blood samples. The quantities of propranolol and atenolol were determined by the high-performance liquid chromatographic (HPLC) method described by Drummer *et al.*,⁶⁾ and Taylor *et al.*,⁷⁾ respectively.

Data Analysis Statistical significance was assessed by using Student's paired *t* test.

Results

Release Tests The *in vitro* release tests of propranolol and atenolol were carried out with hydrogel preparations which were prepared at various concentrations of PVA and at various pH values. Figure 1 shows the effect of PVA concentration on the release profiles of propranolol and atenolol from hydrogel preparations (pH 7.0). Releases of propranolol from hydrogel preparations at 10%w/w and 15%w/w PVA were similar, while that from hydrogel preparation at 20%w/w PVA was slower. The release of atenolol decreased at higher concentrations of PVA in hydrogel preparations.

Figure 2 shows the release profiles of propranolol and atenolol from hydrogel preparations (10%w/w PVA) at pH 6.5, 7.0 and 8.0. The release profiles of both drugs from hydrogel preparations did not change with pH in this range.

Release rate from a swelling polymeric hydrogel can

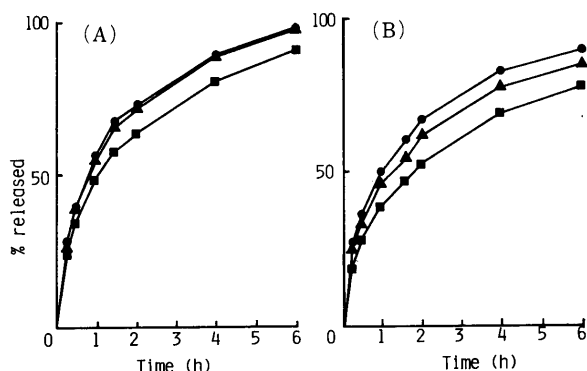


Fig. 1. Release Profiles of β -Blockers from PVA Hydrogel Preparations (pH 7.0) at Various Concentrations of PVA

(A) propranolol-HCl; (B) atenolol. Concentrations of PVA: (●) 10%w/w, (▲) 15%w/w, (■) 20%w/w. Each point represents the mean of 3 experiments.

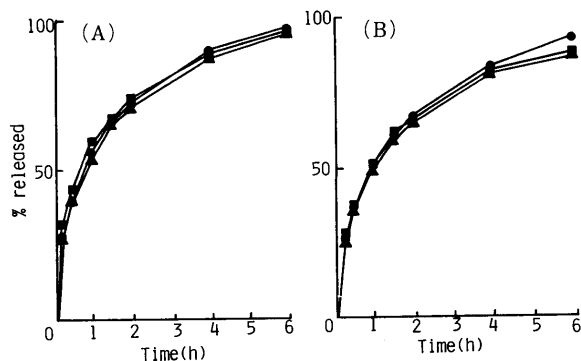


Fig. 2. Release Profiles of β -Blockers from PVA Hydrogel Preparations at Various pH Values

(A) propranolol-HCl; (B) atenolol. pH of hydrogel preparations: (■) pH 6.5, (●) pH 7.0; (▲) pH 8.0. Concentration of PVA is 10%w/w. Each point represents the mean of 3 experiments.

generally be treated by using $M_t/M_\infty = kt^n$ (Eq. 1), where M_t/M_∞ is the fraction of drug released at time t , 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 a non-Fickian diffusion model, and $n=0.5$ corresponds to Fickian diffusion (Higuchi model).⁵⁾ The kinetic parameters, n and k , for β -blockers released from hydrogel preparations were calculated from the slope and the intercept point, respectively, of a plot based on $\log(M_t/M_\infty) = n \log t + \log k$ (Eq. 2). These parameters are listed in Tables I and II. The derived n values found for on propranolol and atenolol approached 0.5. The releases of both drugs from the hydrogel preparations followed the well-known Fickian diffusion model. Therefore, if the cumulative amounts of released propranolol and atenolol from hydrogel preparations were plotted as a function of square root of time, the release profiles would show one straight line.

Rectal Administration Figure 3 shows the plasma concentrations of propranolol and atenolol after rectal administration of hydrogel preparations at various concentrations of PVA and suppositories (Witepsol H-15) in rats. The

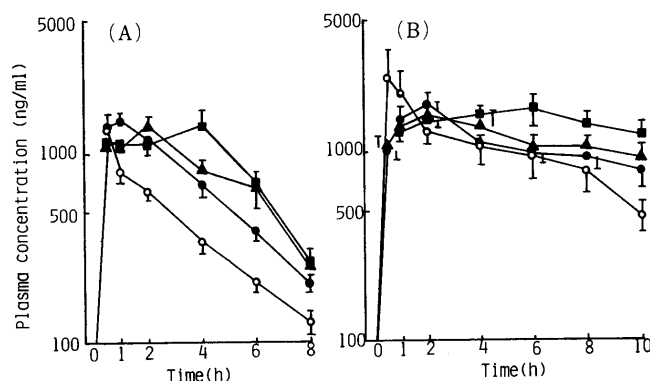


Fig. 3. Plasma Concentrations of β -Blockers after Rectal Administration of PVA Hydrogel Preparations (pH 7.0) at Various Concentrations of PVA and Suppositories in Rats

(A) propranolol-HCl (10 mg/kg); (B) atenolol (20 mg/kg). Concentrations of PVA: (●) 10%w/w, (▲) 15%w/w, (■) 20%w/w; (○) suppository (Witepsol H-15). Each point represents the mean \pm S.E. of 4 animals.

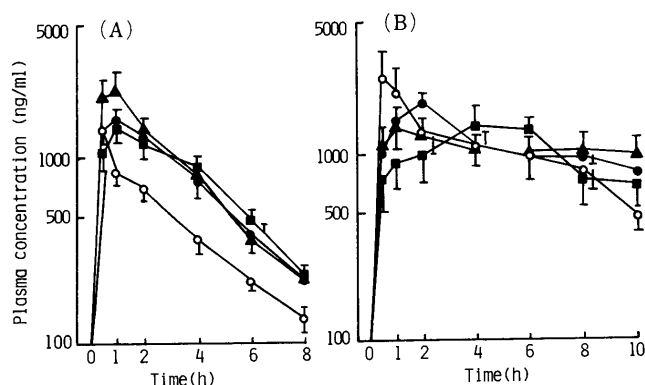


Fig. 4. Plasma Concentrations of β -Blockers after Rectal Administration of PVA Hydrogel Preparations at Various pH Values and Suppositories in Rats

(A) propranolol-HCl (10 mg/kg); (B) atenolol (20 mg/kg). pH of hydrogel preparations: (■) pH 6.5, (●) pH 7.0, (▲) pH 8.0, (○) suppository (Witepsol H-15). Concentration of PVA was 10%w/w. Each point represents the mean \pm S.E. of 4 animals.

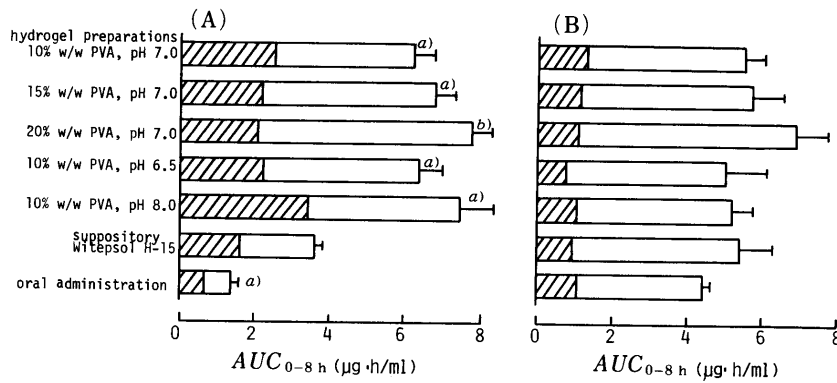


Fig. 5. Bioavailabilities of β -Blockers after Rectal Administration of PVA Hydrogel Preparations in Rats

(A) propranolol-HCl (10 mg/kg); (B) atenolol (20 mg/kg). The AUC was calculated using the trapezoidal rule. The striped bar (\square) represents AUC_{0-2h} . *a*) Significantly different from the suppository at $p < 0.005$. *b*) Significantly different from the suppository at $p < 0.001$. Each point represents the mean \pm S.E. of 4 animals.

TABLE I. Kinetic Parameters for Propranolol-HCl Release from Hydrogel Preparations

Preparation	Release exponent <i>n</i>	Kinetic constant <i>K</i> (% \cdot min ⁻ⁿ)	Correlation coefficient <i>r</i>
10% PVA (pH 7.0)	0.486	7.691 \pm 0.065	0.999
15% PVA (pH 7.0)	0.493	7.269 \pm 0.122 ^{a)}	0.999
20% PVA (pH 7.0)	0.500	6.288 \pm 0.141 ^{b)}	0.999
10% PVA (pH 6.5)	0.477	7.834 \pm 0.200	0.999
10% PVA (pH 8.0)	0.513	7.295 \pm 0.301	0.998

a) Significantly different from the preparation with 10% PVA (pH 7.0) at $p < 0.05$. *b*) Significantly different from the preparation with 10% PVA (pH 7.0) at $p < 0.001$.

TABLE II. Kinetic Parameters for Atenolol Release from Hydrogel Preparations

Preparation	Release exponent <i>n</i>	Kinetic constant <i>K</i> (% \cdot min ⁻ⁿ)	Correlation coefficient <i>r</i>
10% PVA (pH 7.0)	0.444	8.299 \pm 0.098	0.998
15% PVA (pH 7.0)	0.450	7.534 \pm 0.072 ^{d)}	0.999
20% PVA (pH 7.0)	0.491	5.212 \pm 0.100 ^{b)}	0.999
10% PVA (pH 6.5)	0.440	8.780 \pm 0.152	0.998
10% PVA (pH 8.0)	0.474	8.104 \pm 0.099	0.999

a) Significantly different from the preparation with 10% PVA (pH 7.0) at $p < 0.005$. *b*) Significantly different from the preparation with 10% PVA (pH 7.0) at $p < 0.001$.

propranolol plasma concentrations obtained from hydrogel preparations were relatively high at early times after administration and then propranolol was eliminated rapidly from plasma. However, these plasma concentrations were higher than that in the case of the suppository. On the other hand, the atenolol plasma concentration after rectal administration of hydrogel preparations did not show a sharp peak but gave a sustained plateau level during 10 h in contrast to the suppository. The atenolol plasma concentration with 20% PVA was particularly well sustained.

Figure 4 shows the plasma concentrations of propranolol and atenolol after rectal administration of hydrogel preparations at various pH values in rats. The propranolol plasma concentration profiles were similar among pH 6.5, 7.0 and 8.0 hydrogel preparations. These plasma concentrations were higher than that in the case of the suppository. The pH of hydrogel preparations also did not

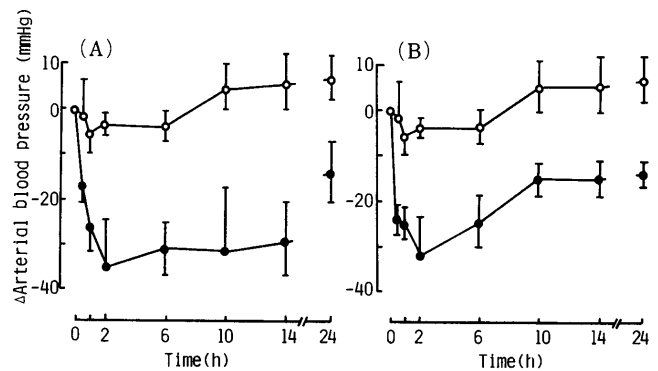


Fig. 6. Change of Arterial Blood Pressure after Rectal Administration of β -Blocker Hydrogel Preparations (10%w/w PVA, pH 7.0) in Rats

(A) propranolol-HCl (10 mg/kg); (B) atenolol (20 mg/kg). (O) PVA hydrogel alone, (●) PVA hydrogel containing β -blocker. Each point represents the mean \pm S.E. of 4 animals.

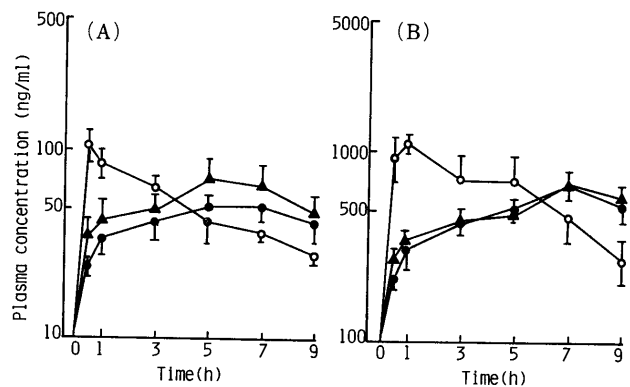


Fig. 7. Plasma Concentrations of β -Blockers after Rectal Administration of PVA Hydrogel Preparations (15%w/w PVA, pH 7.0) in Dogs

(A) propranolol-HCl (100 mg/dog body); (B) atenolol (100 mg/dog body). (●) 1 g hydrogel preparation, (▲) 2 g hydrogel preparation, (○) suppository (Witepsol H-15; 1g). Dose of drug was 100 mg/dog. Each point represents the mean \pm S.E. of 4 animals.

affect the atenolol plasma concentration profiles.

The area under the blood concentration curve (AUC) after rectal administration of the hydrogel preparations of β -blockers in rats is shown in Fig. 5. The mean AUC_{0-8h} value after rectal administration of the propranolol hydrogel preparation (20%w/w PVA, pH 7.0) was 2.16 and 5.29 times higher than those of the suppository (Witepsol H-15) and oral administration, respectively. The mean

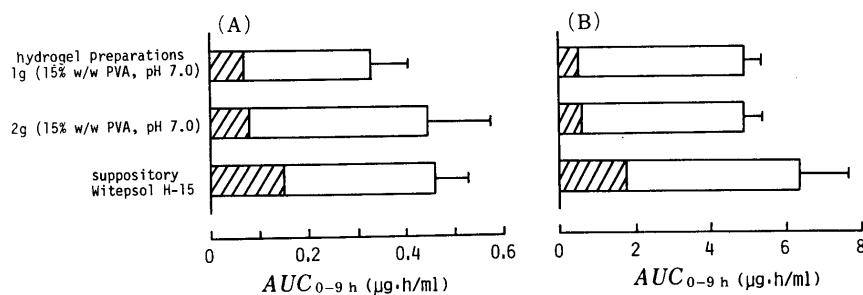


Fig. 8. Bioavailabilities of β -Blockers after Rectal Administration of PVA Hydrogel Preparations in Dogs

(A) propranolol-HCl (100 mg/dog body); (B) atenolol (100 mg/dog body). The AUC was calculated using the trapezoidal rule. The striped bar (\square) represents AUC_{0-2h} . Each point represents the mean \pm S.E. of 4 animals.

AUC_{0-8h} value after rectal administration of the atenolol hydrogel preparation (20%w/w PVA, pH 7.0) was 1.29 and 1.59 times higher than those of the suppository (Witepsol H-15) and oral administration, respectively. Figure 6 shows the change in arterial blood pressure before and after rectal administration of β -blocker hydrogel preparations (10%w/w PVA, pH 7.0) in rats. The arterial blood pressure decreased over 30 mmHg compared with the initial level at 2 h after rectal administration of each of the preparations and these hypotensive effects continued for 24 h.

Figure 7 shows the plasma concentrations of propranolol and atenolol after rectal administration of the hydrogel preparations (1 and 2 g) and the suppository (Witepsol H-15) in dogs. The plasma concentrations of propranolol after rectal administration of the hydrogel preparations did not show a sharp peak but gave a sustained plateau level as compared to the suppository. However, the plasma concentrations of propranolol were relatively low. On the other hand, the plasma concentrations of atenolol were relatively high with hydrogel preparations and the suppository. The plasma concentrations of atenolol with hydrogel preparations did not show a sharp peak and exhibited prolonged action. The plasma concentration with the 2 g propranolol hydrogel preparation was higher than that with the 1 g hydrogel preparation. Atenolol hydrogel preparations did not show a marked difference between the 1 and 2 g hydrogel preparations. The AUC after rectal administration of the hydrogel preparations of β -blockers in dogs is shown in Fig. 8. The mean AUC_{0-9h} values with hydrogel preparations (2 g; 15%w/w PVA, pH 7.0) of propranolol and atenolol were 1.0 and 0.77 times those with the suppositories (Witepsol H-15), respectively. This result in dogs was different from that in rats.

Discussion

PVA hydrogel, prepared by a low-temperature crystallization method in this study, has a porous, three-dimensional network structure with high mechanical strength and high water content. Furthermore, this hydrogel is a non-erodible, non-dissolving and fully swollen matrix.^{3,4} Preparations of β -blockers, propranolol-HCl and atenolol, using this hydrogel were designed to give controlled, transrectal drug delivery. Propranolol is lipid-soluble and undergoes first-pass metabolism by the liver, while atenolol is poorly lipid-soluble and is excreted unchanged in the urine.¹

Several basic studies have shown that drug release from hydrogels depends on the nature of the 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.⁷ Propranolol-HCl and atenolol completely dissolved in the water phase of the hydrogel. In these *in vitro* release tests, the release of propranolol and atenolol from hydrogel preparations followed the Fickian diffusion model (Higuchi model), and the drug release profile versus the square root of time gave a straight line over about 60% of the total release process.⁵ The release exponent n of atenolol was slightly below 0.5. Atenolol is a hydrophilic compound, *i.e.* the partition coefficient of atenolol ($\log K_m = 1.95$ in octanol/pH 7.4 buffer system) is very low as compared with that of propranolol ($\log K_m = 3.37$ in octanol/pH 7.4 buffer system).⁹ These release systems are suitable for the β -blocker, bunitrolol-HCl, which dissolves in the water phase of the hydrogel,⁴ and the release of indomethacin, which is dispersed in the hydrogel,³ as previously described. These results may be due to the characteristics of the hydrogel, which is a non-erodible, porous, and fully swollen matrix.

The release rates of propranolol and atenolol from hydrogel preparations were affected by the concentration of PVA but were not affected by the pH of the preparations. Higher concentrations of PVA resulted in a more extensive network system and lower drug release rates. This result is in agreement with the release characteristics of indomethacin and bunitrolol, as previously described.^{3,4} A lower pH of the hydrogels would result in a higher number of ionized molecules of propranolol ($pK_a = 9.5$) and atenolol ($pK_a = 9.45$)¹¹ in the hydrogels, and this may be why the release rates did not change with the pH of the hydrogel preparations. However, this result does not agree with that for bunitrolol, the release of which increased at a lower pH of the hydrogel preparation, as previously described.⁴

In the rectal administrations of propranolol-HCl and atenolol in rats, these hydrogel preparations gave higher plasma concentrations compared with suppositories. The plasma concentration with hydrogel preparations increased at higher concentrations of PVA in the hydrogel preparations, corresponding to the results of the *in vitro* release tests. The pH of the hydrogel preparations did not affect the plasma profiles of propranolol and atenolol.

The rectal administration of propranolol and atenolol hydrogel preparations in dogs also resulted in prolonged action. However, the drug plasma concentration profiles in dogs were different from those in rats. These results may be due to a smaller relative contact area of the hydrogel preparation with the rectal mucosal surface of dogs com-

pared to that in rats and the hydrogel preparation cannot spread in the rectal lumen as compared to the conventional suppository. Furthermore, the first-pass metabolism of propranolol in the liver¹⁰ and venous drainage in the rectum may be different between rats and dogs.

When the drug is absorbed in the lower parts of the rectum, it may enter the lower and middle rectal veins, finally passing into the inferior *vena cava*, thereby bypassing the portal system and the liver.² A drug absorbed from the upper parts of the rectum will probably be transported *via* the upper rectal veins into the portal system and pass through the liver before entering the systemic circulation. In rats, it has been shown that rectal administration of an aqueous solution of hepatic high-clearance drugs, lidocaine and propranolol resulted in a very substantial increase in systemic availability compared to oral administration.^{11,12} In human subjects, rectal bioavailability of lidocaine solutions resulted in an approximately 100% increase in *AUC* compared to oral administration of the same dose.¹³

In this study, the bioavailability arising from rectal administration of a propranolol suppository increased by approximately 2.5 times compared to oral administration in rats. Furthermore, the bioavailability for rectal administration of propranolol hydrogel preparation increased by over 2 times compared to that for rectal administration of the suppository in rats, because the hydrogel preparation cannot spread in the rectal lumen as the conventional suppository dose.

In conclusion, the rectal administration of β -blockers using PVA hydrogel may be practically useful in the therapeutic treatment of hypertension diseases, offering prolonged action. Furthermore, improved bioavailability of hepatic high-clearance drugs, such as propranolol, should be obtained by rectal administration in PVA hydrogel.

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