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Pharmaceutical Studies of Polyacrylic Acid Aqueous Gel Bases. II.<sup>1)</sup>  
Absorption of Ibuprofen from Gel Preparations  
following Rectal Administration in Rats

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Ibuprofen (IP) gel preparations made by suspending IP in a polyacrylic acid aqueous gel were administered rectally to rats by an *in situ* rectal loop method, and the IP plasma levels were determined. In addition, the IP release rate from gel preparations was examined *in vitro* and the correlation with the *in situ* data was investigated.

In the case of IP gel preparations with a higher viscosity or a lower pH, IP plasma levels were maintained for a longer period and the IP release rate from the gel preparation was small. IP plasma levels reached their peaks between one and two hours. The AUC by rectal administration was not influenced by the viscosity or pH of the gel preparation and was about twice the AUC by oral administration.

Thus, it appears that aqueous polyacrylic acid gels are useful as a base for rectal drug administration; the duration of high IP plasma level can be controlled by changing the viscosity and pH.

**Keywords**—ibuprofen; polyacrylic acid; aqueous gel; rectal administration; anti-inflammatory

### Introduction

Ibuprofen (2-(4-isobutylphenyl)propionic acid; IP) has been widely used as a non-steroidal compound having anti-inflammatory, analgesic and anti-pyretic effects.<sup>3-7)</sup> In the usual oral administration of IP, gastrointestinal disturbance (which is a common side effect of non-steroidal anti-inflammatory compounds) arises.<sup>7,8)</sup> In addition, although oral IP produces immediate onset of action, the duration is unexpectedly short.<sup>3)</sup> Therefore, it is desirable to establish a method of administration with minimal side effects and to develop an IP preparation that provides an effective blood level for a reasonably long time. The rectal administration of an IP suppository with an oleaginous base has been reported to be a useful method of administration.<sup>9,10)</sup>

In the previous study, we administered insulin rectally to rats and rabbits using gel preparations in which a polyacrylic acid aqueous gel (HIVISWAKO 105®) was the base. The results

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demonstrated that insulin was absorbed well.<sup>11)</sup> Polyacrylic acid aqueous gel can be adjusted to a suitable pH, and unpleasantness during rectal administration is minimal.<sup>11)</sup>

In the present study, IP gel preparations were used to obtain prolonged action by taking advantage of these gel characteristics, and the bioavailability of the IP gel preparations was examined after rectal administration.

### Experimental

**Materials**—Polyacrylic acid (HIVISWAKO 105®) was obtained from Wako Pure Chemical Industries, Ltd., and ibuprofen from Kakenkayaku Kako Co., Ltd.

**Ibuprofen Preparation**—The gel was prepared by adding 10% NaOH solution to various concentrations of polyacrylic acid stirred in distilled water to adjust the pH. The pH of the gels was adjusted to 5.0, 6.5 or 8.0. The concentrations of the gels were 0.5, 1.0 and 2.0 w/v%. IP was suspended in each gel base at a concentration of 50 mg/ml.

**Determination of Viscosity**—The viscosities of the gel bases and the gel preparations were measured with a cone plate viscometer (E type, Tokyo Keiki)<sup>11)</sup> at 37° and 10 rpm.

**Release Experiments**—The release rate of IP from the gel preparations was measured with a suppository release apparatus (Toyama Sangyo, Ltd.) according to the method of Muranishi *et al.*<sup>12)</sup> The gel preparation (5 ml) in a cylindrical cell was separated from the extraction phase by a membrane filter. The release phase was phosphate buffer (pH 7.4), which was stirred at 100 rpm. The membrane filter used was an FR-250 microfilter (Fuji Photo Film Co., Ltd.); it prevents leakage of the gel base into the release phase. In the experiments using gel preparations with various pH values, the preparations were slowly stirred (50 rpm) to simulate rectal conditions, but in the experiments using gel preparations with various viscosity values, stirring was not done.

**Animal Experiments**—Wistar strain albino male rats weighing 230–260 g were used, and were fasted for 15 hr prior to the experiments. Rats were anesthetized with pentobarbital, then IP gel preparations were administered either by an *in situ* rectal loop method, in which the abdomen was opened and IP gel preparations were administered to the rectum 5 cm above the anus, or by oral administration. IP gel preparations were given at a dosage of 4 ml/kg of body weight. Blood samples (0.5 ml) were withdrawn from the inguinal vein at 0.5, 1, 2, 3, 5 and 7 hr after drug administration.

**Assay Procedure for Ibuprofen**—The quantity of IP was determined by the gas chromatographic method of Iguchi *et al.*<sup>13)</sup> Gas chromatography was carried out with a Shimadzu GC-4CMPF gas chromatograph, and diethyl phthalate was used as an internal standard.

**Calculation of the AUC**—The AUC was calculated according to the method of Kaplan by means of the trapezoidal rule.<sup>14)</sup>

### Results

#### Viscosity Characteristics of IP Gel Preparations

The viscosity characteristics of the polyacrylic acid aqueous gel bases (pH 5.0, 6.5 or 8.0) and the gel preparations made by suspending IP (50 mg/ml) in gel bases are shown in Fig. 1. The viscosity of the gel base increased with increase in the concentration of polyacrylic acid. The gel bases of pH 5.0, 6.5 and 8.0 had similar viscosities, that is, the viscosity of the gel base was not influenced by pH. In contrast, the viscosity of the gel preparation made by suspending IP in each gel base was lower than that of the corresponding gel base itself, and the degree of the viscosity reduction became larger as the pH of the gel base was made higher.

#### *In Vitro* Release Experiments

The results of release experiments for gel preparations (pH 6.0) with various concentrations of polyacrylic acid are shown in Fig. 2. The gel preparations were not stirred because dynamic effects on the viscosity induced by stirring the gel would have to be taken into consideration. The higher the concentration of polyacrylic acid (namely, the higher the viscosity),

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13) S. Iguchi, M. Yamamoto, T. Goromaru and K. Yamashita, *Yakuzaigaku*, **27**, 10 (1967).

14) S.A. Kaplan, *J. Pharmacokin. Biopharm.*, **1**, 212 (1973).

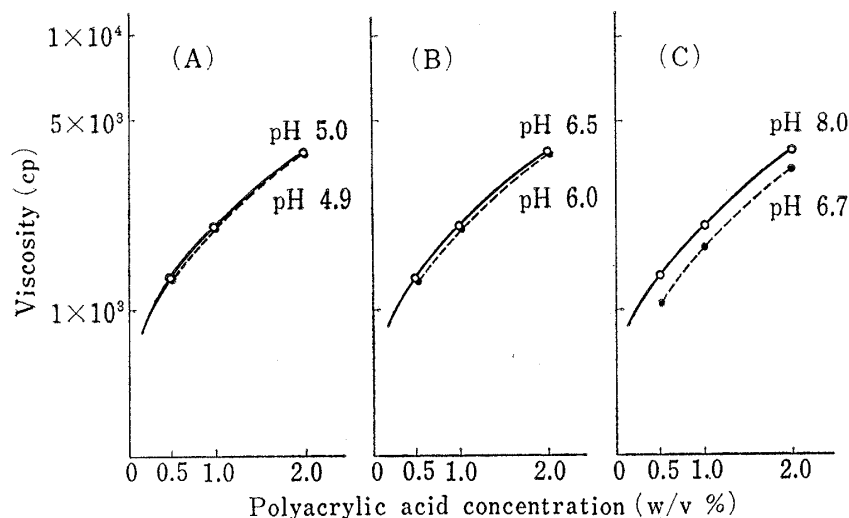


Fig. 1. Relationships among Polyacrylic Acid Concentration, Viscosity and pH in Various Gel Bases and IP Gel Preparations

The viscosities of gel bases (—○—) and IP gel preparations (—●—) were measured with a cone plate viscometer (E type) at 37° and 10 rpm. The pH values of gel bases were pH 5.0 (A), pH 6.5 (B) and pH 8.0 (C). IP gel preparations were prepared with each gel base by suspending IP (50 mg/ml of gel). Viscosity is plotted semilogarithmically as a function of the concentration of polyacrylic acid.

the slower was the IP release from the gel preparations. The results of release experiments for gel preparations (1%) with various pH values are shown in Fig. 3. The preparations were stirred at 50 rpm to simulate rectal conditions. IP release was slower at lower pH. These results indicate that higher viscosity or lower pH of the gel preparations delayed IP release.

#### Plasma Concentrations following Administration of Gel Preparations

Fig. 4 shows the plasma IP concentrations after the rectal administration of gel preparations (pH 6.0) with various viscosities to rats. In the case of the 2.0% gel preparation (pH 6.0), where the viscosity is highest, the peak plasma concentration was 174.5  $\mu\text{g}/\text{ml}$ , which was lower than that of the 0.5 or 1.0% gel preparation. However, the plasma concentration at 7 hr, 64.0  $\mu\text{g}/\text{ml}$ , was higher than with the other preparations.

Plasma IP concentrations after the rectal administration of gel preparations (1%) with various pH values to rats are shown in Fig. 5. The gel preparation of pH 6.7 showed a peak plasma concentration of 254.0  $\mu\text{g}/\text{ml}$  after one hour, but later the concentration decreased rapidly, and the plasma concentration after five hours was about a quarter of the peak value. On the other hand, although the gel preparation of pH 4.9 did not show a marked peak plasma concentration, the plasma concentration was 130.0  $\mu\text{g}/\text{ml}$  even after five hours. Thus, it is evident that the gel preparation of pH 4.9 had a more prolonged action than that of pH 6.7.

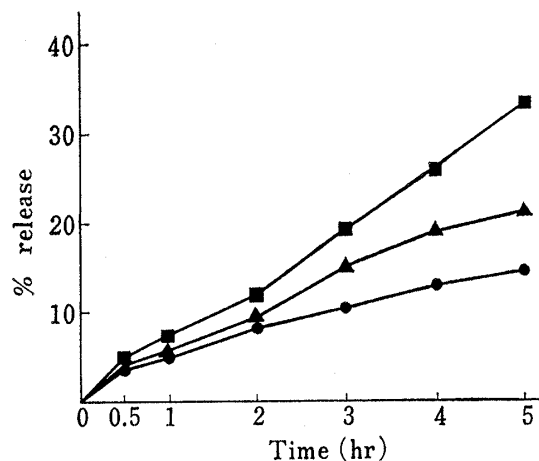


Fig. 2. Effect of the Concentration of Polyacrylic Acid on IP Release from Gel Preparations

The polymeric concentrations of IP gel preparations were 0.5% (—■—), 1.0% (—▲—), and 2.0% (—●—). Each value represents the mean of 6 experiments.

Fig. 6 shows the plasma IP concentration produced by gel preparations (1%, pH 6.0) administered rectally in comparison with those administered orally. The peak plasma concentrations occurred after one hour in both rectal and oral administrations. The AUC for rectal administration was about twice as large as the AUC for oral administration. In addition,

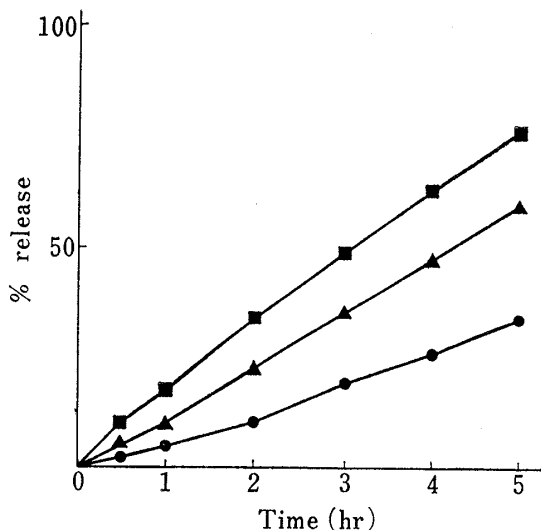


Fig. 3. Effect of pH on the Release of IP from Gel Preparations

The pH values of IP gel preparations were pH 6.7 (—■—), pH 6.0 (—▲—), and pH 4.9 (—●—). Each value represents the mean of 6 experiments.

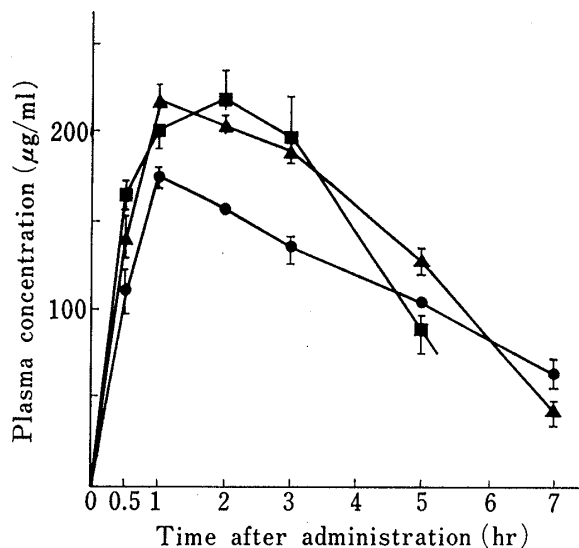


Fig. 4. Effects of Various Concentrations of Polyacrylic Acid on Plasma Concentrations of IP after Rectal Administration of the Gel Preparations in Rats

The polymeric concentrations of IP gel preparations were 0.5% (—■—), 1.0% (—▲—), and 2.0% (—●—). IP gel preparations (IP 50 mg/ml of gel with pH 6.5) were administered in a volume of 4 ml/kg body weight. Each value represents the mean  $\pm$  S.E. of 6 rats.

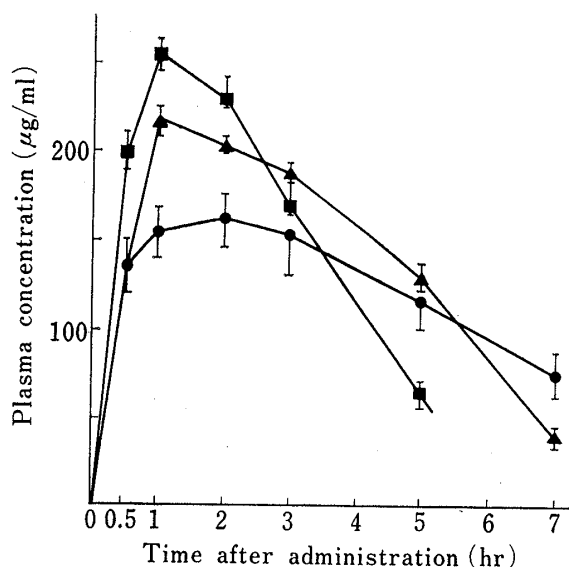


Fig. 5. Effect of Gel pH on Plasma Concentrations of IP following Rectal Administration of the Gel Preparations

The pH values of IP gel preparations were pH 6.7 (—■—), pH 6.0 (—▲—), and pH 4.9 (—●—). IP gel preparations (IP 50 mg/ml of gel with 1%) were administered in a volume of 4 ml/kg body weight. Each value represents the mean  $\pm$  S.E. of 6 rats.

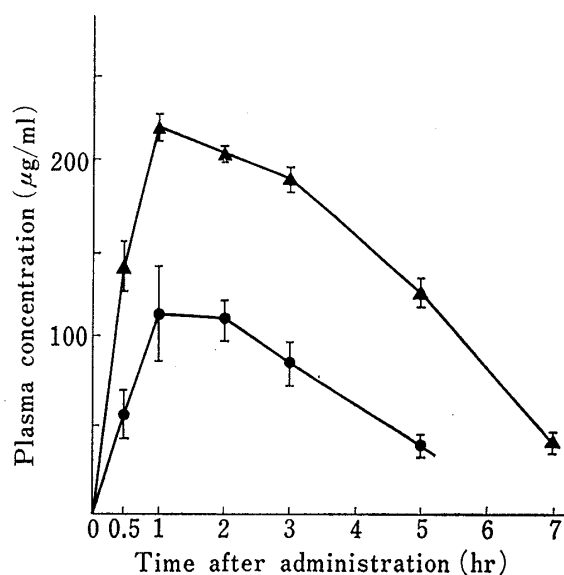


Fig. 6. Plasma Concentrations of IP following Oral or Rectal Administration of Gel Preparations in Rats

IP gel preparations (IP 50 mg/ml of gel, pH 6.5 and 1%) were administered in a volume of 4 ml/kg body weight, orally (—●—), or rectally (—▲—). Each value represents the mean  $\pm$  S.E. of 6 rats.

TABLE I. Bioavailability of Various IP Gel Preparations in Rats

IP gel preparation <sup>a)</sup>	AUC <sup>b)</sup> ( $\mu\text{g hr/ml}$ )	Peak level <sup>b)</sup> ( $\mu\text{g/ml}$ )	Peak time <sup>b)</sup> (hr)
	Oral administration		
1.0%, pH 6.0	425.4 $\pm$ 47.4****	129.2 $\pm$ 24.8****	1
	Rectal administration		
0.5%, pH 6.0	943.8 $\pm$ 71.2*	222.5 $\pm$ 14.8*	2
1.0%, pH 6.0	1108.4 $\pm$ 24.0	217.7 $\pm$ 3.5	1
2.0%, pH 6.0	1027.6 $\pm$ 28.0*	174.5 $\pm$ 4.6**	1
1.0%, pH 4.9	1148.8 $\pm$ 147.5*	184.0 $\pm$ 14.7**	2
1.0%, pH 6.0	1108.4 $\pm$ 24.0	217.7 $\pm$ 3.4	1
1.0%, pH 6.7	872.3 $\pm$ 40.5***	216.3 $\pm$ 5.5***	1

a) IP gel preparations (IP 50 mg/ml of gel) were administered in a volume of 4 ml/kg body weight.

b) Each value represents the mean  $\pm$  S.E. of 6 rats. Statistical significance of differences from the IP gel preparation of 1.0% and pH 6.0 is follows: \* not significant, \*\*  $p < 0.05$ , \*\*\*  $p < 0.01$ , \*\*\*\*  $p < 0.0005$ .

the individual differences on rectal administration were obviously small compared with those on oral administration.

Bioavailability data determined from the above experimental observations are summarized in Table I. Peak plasma concentrations were found after one to two hours, and in the case of rectal administration, the AUC was not influenced by the viscosity or the pH of the gel preparations; the value was almost constant at 1000  $\mu\text{g}\cdot\text{hr/ml}$ .

### Discussion

Fig. 1 shows that the viscosity of IP gel preparations made by suspending IP in gel base is lower than that of the corresponding gel base itself. The pH of IP gel preparations falls below that of the gel base (pH 5.0 to 4.9, pH 6.5 to 6.0 and pH 8.0 to 6.7), and the degree of the pH decrease is larger for a gel base with a higher pH. It is generally recognized that as the carboxyl groups of the polymer chain in a polyacrylic acid aqueous gel become less ionized, the mutual repulsive forces of the electric charges decrease so that the viscosity of the gel decreases.<sup>15)</sup> Therefore, we can speculate that when IP, which is a weakly acidic drug ( $pK_a$  4.3), is suspended in a gel, the degree of ionization of the polymer falls on dissolving IP in the gel, and consequently the viscosity of the gel should decrease. As more IP is dissolved in a gel preparation of pH 8.0 than one of pH 5.0, it is reasonable that the degree of viscosity reduction of gel preparations of pH 8.0 should be larger than that of gels of pH 5.0.

In the *in vitro* release experiments, the effect of the gel concentration (namely, viscosity difference) was evident; the higher the viscosity of the gel, the slower IP release was (Fig. 2). Spang-Brunner and Speiser reported that the drug release from high viscosity gel preparations was slower than that from low viscosity gel preparations in *in vitro* experiments on resorcinol release from aqueous gel preparations,<sup>16)</sup> and their results are consistent with ours in this respect. On the other hand, in the *in situ* rectal administration of IP gel preparations to rats, the plasma IP level tended to be prolonged in the case of high viscosity gel preparations (Fig. 4). From these observations, it is considered that the slower IP release from a gel preparation with high viscosity is reflected in more prolonged IP absorption from the rectum.

As the pH of the gel preparation was lowered, the *in vitro* IP release was delayed (Fig. 3). It seems that an increase in the viscosity upon lowering the pH of the gel preparation (Fig. 1) has some influence, as discussed above. Moreover, the fact that IP is a weakly acidic drug ( $pK_a$  4.3) might have an additional effect. In other words, since IP in gel preparations of pH

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16) B.H. Spang-Brunner and P.P. Speiser, *J. Pharm. Pharmacol.*, **28**, 23 (1976).

6.7 is more ionized than in preparations of pH 4.9, the IP release from preparations of pH 6.7 is more rapid than that from gel preparations of pH 4.9. As is evident from Fig. 5, the results of *in situ* absorption experiments at various pH's again coincide with the *in vitro* ones. That is, at lower pH, where IP release was slower, IP absorption was also slower and the plasma level was maintained for longer. These results suggest that the IP release rate from gel preparations is rate-limiting in the rectal absorption of IP from these gel preparations in rats.

As regards the bioavailability of IP following rectal administration of the various gel preparations, the AUC was almost the same in gel preparation with various viscosities or pH values (Table I). Thus, IP gel preparations might be able to overcome the transient strong absorption of IP and to maintain reasonable plasma levels for longer periods without changing the overall bioavailability.

Iwamoto *et al.* reported that when an IP suppository with an oleagious base was administered to rats and rabbits, the absorption was almost equal to that in the case of oral administration.<sup>10)</sup> However, the results of our experiments with a polyacrylic acid aqueous gel base showed that the extent of IP absorption after rectal administration was larger than that after oral administration (Fig. 6). On the other hand, Kerckhoffs and Huizinga reported that smaller inter-individual differences in plasma level were obtained by rectal administration than by oral administration,<sup>17)</sup> which is similar to the result of our experiments. Therefore, it appears that rectal administration of the IP preparation was superior to oral administration.

Consequently it is considered that IP preparations using a polyacrylic acid aqueous gel base may be practically useful as a rectal preparation with reduced side effects (which are a result of transient strong absorption of IP) and with prolonged action, which can be modified by controlling the viscosity or pH of the gel.

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