DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 13(7), 1293-1305 (1987)

IN VITRO RELEASE AND RECTAL ABSORPTION OF BARBITAL AND AMINOPYRINE FROM AQUEOUS POLYACRYLIC ACID GEL

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ABSTRACT

This study was designed to evaluate aqueous polyacrylic acid gel (Carbopol gel), relative to its suitability for use as a vehicle for drug delivery. Barbital-Na and aminopyrine, used as model acidic and basic drugs, were completely dissolved into the aqueous gel base at 5 mg/ml and 50 mg/ml, respectively. In the release experiment using micropore membrane, higher concentration of polyacrylic acid in the gel resulted in higher viscosity, and consequently lower release rates of both drugs. Higher pH of barbital gel preparation resulted in higher fraction of ionized molecules of barbital in the gel preparation causing a higher barbital release rate. While the release rate of aminopyrine from gel preparation was the lowest at the region of pH 6.8, the ionized molecules of aminopyrine in gel base was 98.5%. The rectal absorption of barbital from the gel preparation at the pH 5.8-8.3 range had relation with the results of permeability through artificial intestinal lipid barrier and accorded with pH partition

hypothesis. The permeability rate of aminopyrine through the artificial intestinal lipid barrier and the rectal absorption of aminopyrine from gel preparations did not have a marked difference at the pH 5.8-8.3 range. The release of both drugs from gel base was not a rate-limiting factor on the rectal absorption of both drugs from the gel bases.

INTRODUCTION

In pharmaceutical practice, the aqueous gel base uses polyacrylic acid (Carbopol), which is a group of carboxyvinyl polymers cross-linked with allyl sucrose. It has been focused as a dosage form for the drug delivery to body surface and cavities. Sience the gel dissolves in body secretions and is adsorbed in body surface, it is particularly sitable for the administration of some drugs. Today, however, aqueous polyacrylic acid gel base is only applied as an ointment base. In our previous paper, the rectal administration of non-steroidal anti-inflammatory drugs, ibuprofen (1), flurbiprofen, ketoprofen, indomethacin (2) and diclofenac-Na (3), have been reported to be an effective method of administration. Furthermore, this gel base is effective on rectal administration of polypeptides such as insulin (4) and calcitonin (5).

The present study was designed to investigate the physicochemical factors involved in the release of drugs from polyacrylic acid gel bases. Barbital-Na and aminopyrine were used as model acidic and basic drugs. Furthermore, the absorption of barbital-Na and aminopyrine from polyacrylic acid gel in rat rectum was investigated.

MATERIALS AND METHODS

Materials: Polyacrylic acid (Carbopol 941) was obtained from B.F.Goodrich, OH, USA. Barbital-Na and aminopyrine were

obtained from commercially available sources. All other chemicals used were of reagent grade.

Preparations: Polyacrylic acid gel base was prepared by presoaking polyacrylic acid in distilled water for 15 hours at room temperature, and adding 10% NaOH solution to adjust the pH of gel bases. The final concentration of polyacrylic acid in gel base was adjusted by the addtion of water as described in our previous paper (4). The concentration of polyacrylic acid in gel bases were 0.1 and 1% w/v and the pH values selected for study were 4.5, 6.5 and 8.0. Barbital-Na and aminopyrine were dissolved in each gel base at concentration of 5 mg/ml and 50 mg/ml, respsctively. The pH values of gel preparation changed from pH 4.5 to 5.2, from 6.5 to 6.8 and from 8.0 to 8.3 after barbital was dissolved in gel base. The pH values of that which aminopyrine was dissolved, changed from 4.5 to 5.8, from 6.5 to 6.8 and 8.0 to 8.3. The viscosity of gel preparation was measured with a cone and plate viscometer (E type, Tokyo Keiki, Tokyo, Japan) at 37°C. The preparations were stored in dark at 6°C.

In Vitro Release Experiments: The release of drug from the gel preparation at 37°C was determined by using a dissolution-test apparatus for suppository (Toyama Sangyo, Tokyo, Japan), in accordance with the method of Muranishi et al. (6). Two hundred ml of distilled water (the dissolution medium) was put into a releasing glass vessel and maintained at 37°C under stirring at 100 rpm. A 2 ml gel preparation was placed on a micropore membrane (pore size 2.5 um; FR 250, Fuji Photo Film, Tokyo, Japan), fitted at the lower end of a plastic cylindrical cell. The preparation phase was not stirred. An aliquot of 1 ml of dissolution medium was taken and the medium was replenished with the same volume of distilled water. The quantity of drug released from the gel preparation was plotted against the square root of time, and the release rate (μg/ml) was calculated from the slope of the straight line obtained.

In vitro Premeability Experiments: In vitro permeability experiments were carried out by the same manner as described for the release experiments. A membrane used membrane filter (SM 16754: Sartorus, Gottingen, W-Germany) containing artificial intestinal lipid barrier (SM 16750: Sartorus, Gottingen, W-Germany). The medium of receive phase used phosphate buffer (pH 6.8).

Rectal Absorption Experiments: Wistar strain male rats weighing 270-300 g were fasted for 17 hours prior to the experiments. Rats were anesthetized with urethane (4.5 ml/kg body weight ip, 25% w/v ethylcarbamate in distilled water) and pentobarbital-Na (50 mg/kg body weight ip) on rectal absorption experiments of barbital and aminopyrine, respectively. In situ loop method; Barbital and aminopyrine gel preparations were administered into rectal loop (5 cm section above anus), which was isolated by ligation. The doses of barbital and aminopyrine were 10 mg/kg body weight and 100 mg/kg body weight, respectively, and the dosage volume of the preparation was 2 ml/kg body weight. Blood samples (0.6 ml) were collected from the inguinal vein at appropriate times after administration. In situ recirculation method; The rectal absorption of barbital and aminopyrine from isotonic phosphate buffer (pH 4.5, 6.5 and 8.0) was examined by in situ recirculation method in rats. The concentration of barbital and aminopyrine in the perfusate was 0.1 mM. The perfusate (50 ml) was recirculated at the rate of 2 ml/min. The amount of drug disappered from the perfusate was calculated at the difference between the concentration of drug in the initial and the final solutions.

Assay Procedure: The quantity of barbital was determined by the UV spectrophotometric method (240 nm) of Goldbaum et al. (7). The quantity of aminopyrine was determined by UV spectrophotometric method (260 nm) of Brodie et al. (8).

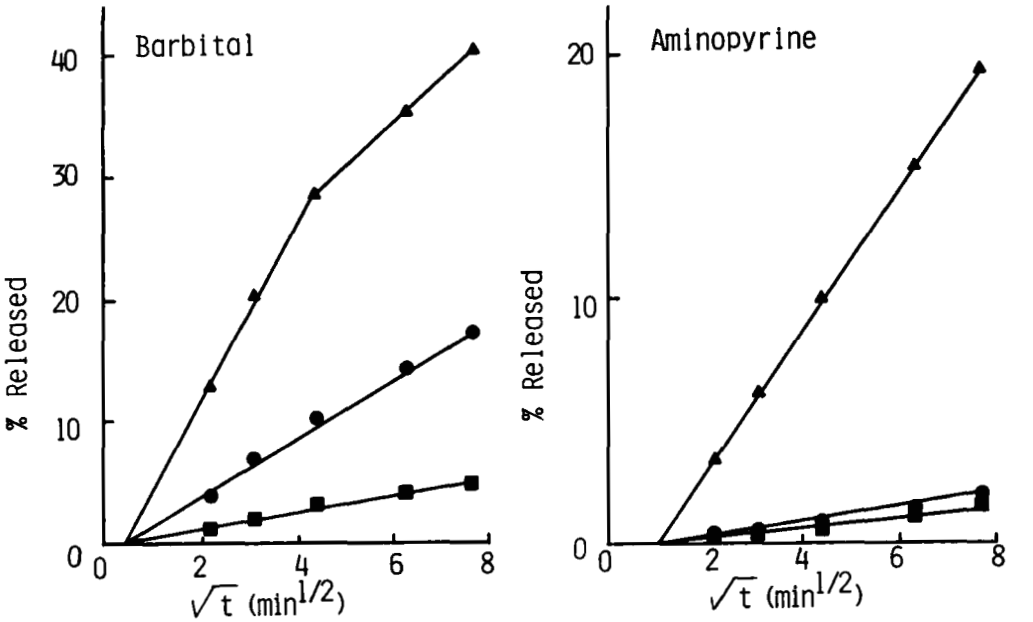

Fig. 1 Effect of Concentration (Viscosity) of Polyacrylic Acid in Aqueous Gel Base on the Release Rate of Barbital and Aminopyrine from Gel Preparations (pH 6.8) through Micro Pore Membrane at 37°C
The concentration of polyacrylic acid were 0.1% w/v (▲), 1% w/v (●) and 2% w/v (■).

RESULTS

Release Experiments: Release of drugs completely dissolved in aqueous polyacrylic acid gel was studied by using micropore membrane and receptor solution. Drug release profiles for gel preparation, expressed as percents release as a function of the square root of time, were plotted. Effect of concentration of polyacrylic acid in the gel base, ie, viscosity effect, on release of barbital and aminopyrine from gel preparation was examined (Fig. 1). Linear relationships between the percent release and the square root of the time were obtained on the

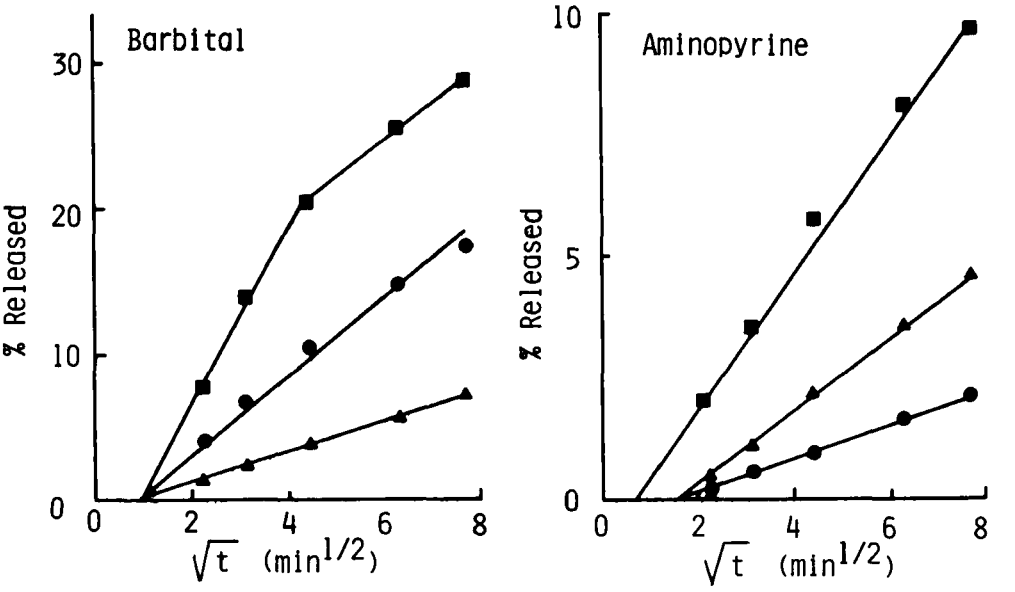

Fig. 2 Effect of pH of Gel Preparation on the Release of Barbital and Aminopyrine from Polyacrylic Acid Gel through Micro Pore Membrane at 37°C
The pH of barbital gel prepapations were 5.2 (▲), 6.8 (●) and 8.3(■).The pH of Aminopyrine gel preparations were 5.8 (▲), 6.8 (●) and 8.3 (■). The concentration of polyacrylic acid in gel base was 1% w/v.

release of both drugs. The release of both drugs accorded with the Higuchi equation (9). The higher the polyacrylic acid concentration, ie, the higher the viscosity and the slower release of both drugs from the gel bases. However, the release rates of aminopyrine between 1% w/v and 2 % w/v polyacrylic acid gels had not a significant diffrence.

Effect of pH of polyacrylic acid gel on release of barbital and aminopyrine from the gel preparation was examined (Fig. 2). Higher release of barbital was seen with higher pH of gel preparation. Aminopyrine releases were in the following

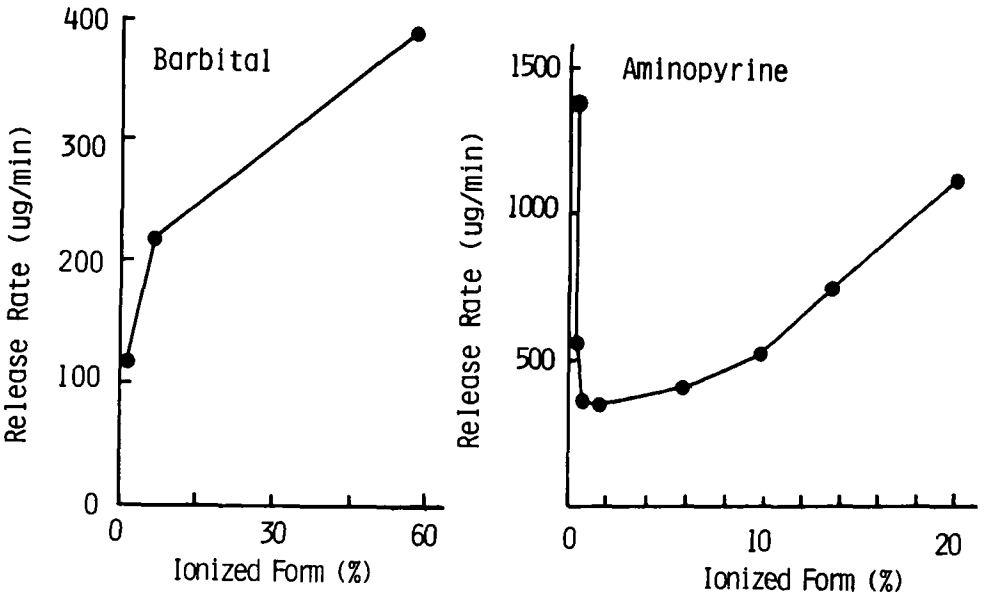

Fig. 3 The Release Rate of Barbital and Aminopyrine from Gel Preparation as Ionized Form (%) of Barbital and Aminopyrine The concentration of polyacrylic acid in gel base was 1% w/v.

order; pH 8.3>pH 5.8>pH 6.8. Furthermore, the aminopyrine release was examined in a more wide range of pH of the gel preparations. Fig. 3 shows plots of the data, expressed as the release rate constant against the percentage of ionized froms for drugs. The pKas of barbital and aminopyrine are 7.8 and 5.0, respectively. The amount of the ionized form of barbital in the gel base was am important factor for the barbital release rate. As aminopyrine was more ionized molecules in the gel base, the release rate of aminopyrine increased. Furthermore, the release rate of aminopyrine also increased on the nonionized molecules more than 98.5% when the gel preparation was at pH 6.8.

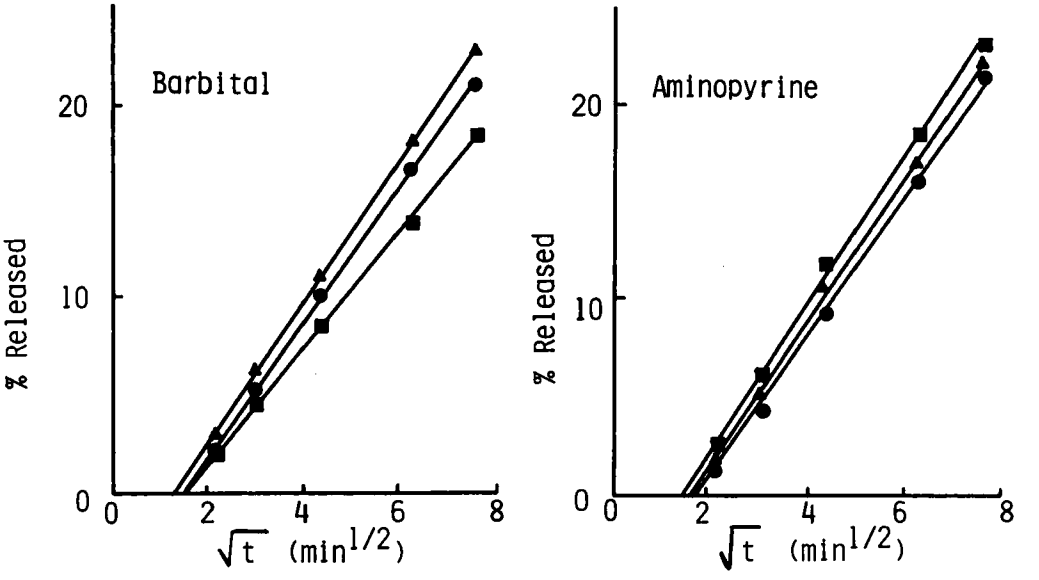

Fig. 4 Effect of pH of Gel Preparation on the Permeability of Barbital and Aminopyrine from Polycarylic Acid Gel through Artificial Intestinal Lipid Barrier
The pH of barbital gel preparation were 5.2 (▲), 6.8 (●) and 8.3 (■). The pH aminopyrine gel preparations were 5.8 (▲), 6.8 (●) and 8.3 (■). The concentration of polyacrylic acid in gel base was 1% w/v.

Permeability Experiments: Effct of pH permeability of barbital and aminopyrine form the polyacrylic acid gel bases thriugh artificial intestinal lipid barrier (Sartorus, lipid barrier D) was examined (Fig. 4). An excellent linear relationship between the permeability of barbital and aminopyrine, and the square root of time was obtained on each pH of gel preparation. The permeability of barbital was in following order; pH 5.2 pH 6.8 pH 8.3. This was not relatived to the results of the release experiment (Fig. 2). Since ionized molecules of barbital in the gel base was higher

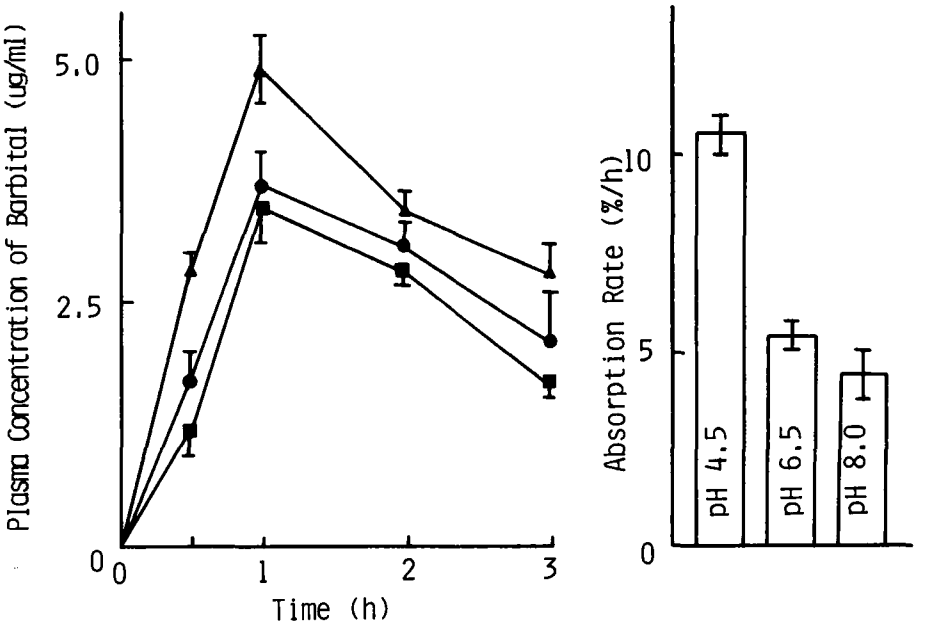

Fig. 5 Plasma Concentration of Barbital following Rectal Administration of Barbital Gel Preparations at Various pH in Rats and Absorption Rates (%/h) of Barbital in Isotonic Buffer at various pH from Rat rectum by In Situ Recirculation Method

The pH of barbital gel preparations were 5.2 (▲), 6.8 (●) and 8.3 (■). The concentration of polyacrylic acid in gel base was 1% w/v. Each value represents the mean ± S.E. of at least 4 rats.

at higher pH, the permeability of barbital through the lipid barrier was lower at higher pH. While the permeability of aminopyrine was in the following order; pH 8.3 > pH 5.8 > pH 6.8, the permeability of aminopyrine was relatived to the partition coefficient of aminopyrine.

Rectal Absorption: The rectal absorption of barbital and aminopyrine from isotonic buffer was accorded with pH partition

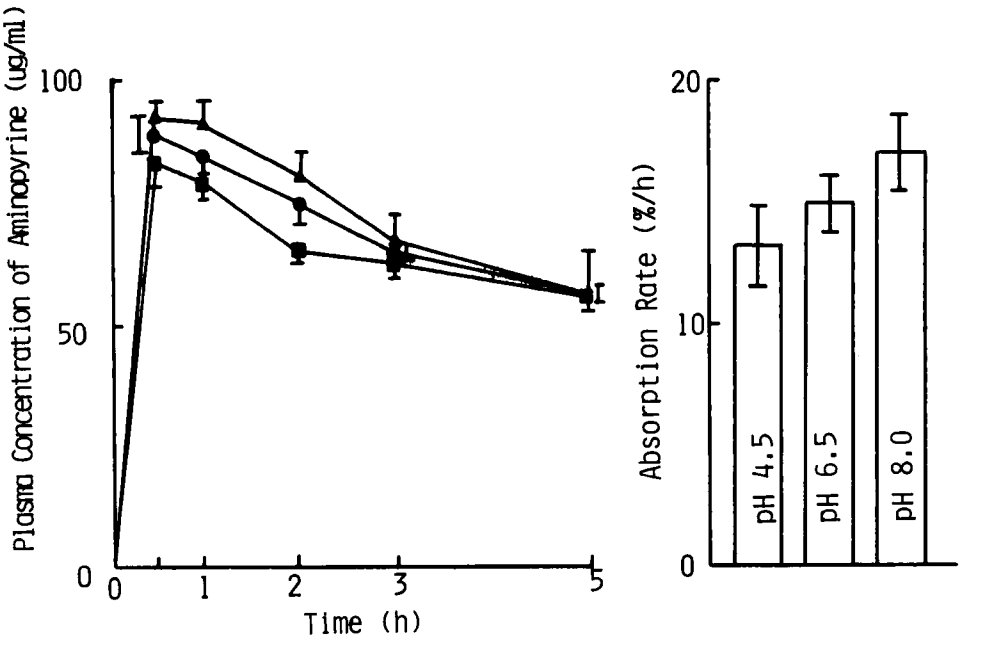

Fig. 6 Plasma Concentration of Aminopyrine following Rectal Administration of Aminopyrine gel preparations at various pH in Rats and Absorption Rates (%/h) of Aminopyrine in Isotonic Buffer at various pH from Rat Rectum by In Situ Recircuration Method

The pH aminopyrine gel preparation were 5.8 (▲), 6.8 (●) and 8.3 (■). The concentration of polyacrylic acid in gel base was 1% w/v. Each value represents the mean ± S.E. of at least 4 rats.

hypothesis (Fig. 5 and Fig. 6). Effect of pH of the gel preparation on the rectal absorption of barbital (Fig. 5) and aminopyrine (Fig. 6) from the gel base was estimated. The barbital concentration in plasma after administration of the gel preparation was in the following order; pH 5.2 pH 6.8 pH 8.3. The rectal absorption of barbital from the gel preparation at various pH accorded with pH partition hypothesis

and related to the result of permeability study through lipid barrier (Fig. 4). However, this result did not relate to the release rate from the gel preperation. While aminopyrine concentration in plasma after rectal administration of the gel preparation was in the following order; pH 5.8 pH 6.8 pH 8.3, however, no significant differences were detected between these concentration area under the curves (AUC).

DISCUSSIONS

The viscosity of polyacrylic acid gel using Carbopol 941 is relatively constant at the wide range of pH 4.5 and pH 12 (4). As barbital-Na and aminopyrine were completely dissolved into the aqueous gel base at 5 mg/ml and 50 mg/ml, respectively, the viscosity of the gel preparation did not change. In the release experiment using the micropore membrane, higher concentration of polyacrylic acid in the gel preparation resulted in higher viscosity and lower release rate of both drugs. This result is also consistent with the release of anti-inflammatory drugs suspended in aqueous polyacrylic acid gel in our previous reports (1-3). On the other hand, the pH of gel preparation affected the release rates of barbital and aminopyrine. Higher pH of barbital gel preparation resulted in higher ionized molecules of barbital in the gel preparation and higher barbital release rate. However, the release rate of aminopyrine from the gel preparation was lowest at the region of pH 6.8, which the aminopyrine ionized molecules in the gel base was 98.5%. Binding of cationic drugs, chlorpheniramine and ephedrin with Carbopol was reported by Elgndy (10). These suggested that some specific interaction between aminopyrine with polyacrylic acid (Carbopol), negatively charged polymer, may be involved. However, there was no evidence of such interaction.

The rectal absorption of barbital and aminopyrine from isotonic phosphate buffer accorded with the pH partition hypothesis. In the case of barbital, the rectal absorption from polyacrylic acid related with the results of permeability rate through lipoid barrier and accorded with the pH partition hypothesis. However, the permeability rate of aminopyrine through the lipoid barrier and the rectal absorption of aminopyrine from the gel preparation was not markedly different from each pH and did not accord with the pH partition hypothesis.

In our previous reports (1-3), the release rate of some anti-inflammatory drugs from the gel preparations, which drugs were suspended in, was a rate limiting factor in the rectal absorption of these drugs in rats. However, the release rates of barbital and aminopyrine from the gel preparations, which drugs completely dissolved in, is not rate-limiting on the rectal absorption of barbital and aminopyrine from the gel preparation in rats.

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