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Evaluation of pH-independent sustained-release granules of dipyridamole by using gastric-acidity-controlled rabbits and human subjects

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Summary

The solubility of dipyridamole at pH 2.5 was about 6000-fold greater than that at pH 7.0. A commercial powder of dipyridamole showed pH-dependent dissolution. Two kinds of sustained-release granules of dipyridamole were prepared. The release rate of pH-dependent sustained-release granules was controlled by ethylcellulose (EC) and decreased with increasing medium pH. The release rate of pH-independent sustained-release granules was regulated by carboxymethylethylcellulose (CMEC), hydroxypropyl methylcellulose (TC-5) and Eudragit RS100, and was not influenced by varying pH of the medium. We used gastric-acidity-controlled rabbits to evaluate the variability in absorption after oral administration of these formulations. An extremely large difference in bioavailability between the high and low gastric acidity groups was observed after oral administration of the commercial powder. There were no statistically significant differences in the values of C_{max}, T_{max}, AUC_{0-12h} and MRT between the high and low gastric acidity groups after administration of pH-independent sustained-release granules, while statistically significant differences in C_{max} and AUC_{0-12h} were found between the two groups after administration of pH-dependent sustained-release granules. Furthermore, this pH-independent sustained-release granule preparation was administered orally to human subjects and compared with the commercial powder. There was no significant difference in the AUC_{0-12h} between the two preparations. It was also shown that the C_{max} for the granules was about 50% of that for the commercial powder and that the plasma levels after oral administration of the granules were maintained over a longer duration than those of the commercial powder. It was found that the bioavailability was not influenced by variations in gastric acidity in rabbits and high bioavailability was achieved in human subjects after oral administration of the pH-independent sustained-release granule preparation, indicating that this preparation should be a useful dosage form for the potential reduction of interindividual variabilities in absorption.

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Introduction

Most drugs are administered orally in solid dosage forms, and dissolution must proceed for

absorption to occur. Generally, incomplete dissolution of a solid drug not only reduces the amount absorbed but also increases the variability in absorption, and as such is a cause for concern in drug therapy. The solubility of a basic drug which is slightly soluble in water, such as dipyridamole, is altered to a considerable extent by the pH of different digestive fluids. Namely, dipyridamole dissolves readily in the stomach, while incomplete dissolution occurs in the intestine. Dipyridamole is known to exhibit considerable interindividual differences in both plasma concentrations and bioavailability (Mahony et al., 1983; Arafat et al., 1989), since it is probably only poorly soluble at neutral pH. Therefore, the gastrointestinal (GI) absorption of dipyridamole is considered to be governed primarily by the extent to which it undergoes dissolution in the stomach.

Although gastric acidity in humans is well known to show a pH value near 1.0, on the basis of subjects with normal or hyperacidity, the effects of a number of factors on the value of the gastric pH cannot be ignored, e.g., elevation to neutral values due to achlorhydria, administration of antacids (Deering and Malagelada, 1977; Garty and Hurwitz, 1980) and H_2-receptor antagonists (Dammann et al., 1982; Fimmel et al., 1985), and eating (Fimmel et al., 1985). Gastric emptying is also influenced by several factors such as eating (Davis et al., 1984) or coadministration of drugs (Nimmo et al., 1973). Thus, gastric emptying may also result in drastic changes in the rate of drug dissolution as well as in gastric acidity, since a large difference exists between the pH values in the stomach and small intestine. Therefore, it is considered that the bioavailability of certain dosage forms, which exhibit in vitro pH-dependent dissolution characteristics, may be altered due to variations in gastric acidity or gastric emptying.

Sustained-release dosage forms are more strongly affected by physiological factors in the GI tract than are rapid-release types, since the former release drug in the GI tract over a longer period of time as compared to the latter. Therefore, the elucidation of the relationship between the physiological factors and the bioavailability of sustained-release dosage forms is essential. A number of studies have evaluated the effect of gastric pH on the bioavailability of sustained-release dosage forms (Berardi et al., 1988; Vashi and Meyer, 1988; Kohri et al., 1989; Yamada et al., 1990). When dipyridamole is prepared as a sustained-release dosage form according to traditional techniques, such as coating with a hydrophobic polymer or granulation by using a hydrophobic polymer as a binding agent, the absorption of drug by the GI tract is considered to be influenced by the gastric acidity or the gastric residence time, which varies both intra- and interindividually. This may be ascribed to the pH-dependent release of such preparations.

The present investigation was aimed at the preparation of a pH-independent sustained-release dosage form of dipyridamole, the evaluation of the influence of gastric acidity on the bioavailability of dipyridamole and the prolongation of plasma levels after oral administration of the preparation to gastric-acidity-controlled rabbits and human subjects, respectively.

Materials and Methods

Materials

Dipyridamole (Sigma Chemical Co., St. Louis, MO), dipyridamole commercial powder (Anginal®, Yamanouchi Pharmaceutical Co., Ltd), carboxymethylethylcellulose (CMEC® AQ, Freund Ind., Co., Ltd), hydroxypropyl methylcellulose (TC-5®, JP-XI grade, Shin-Etsu Chemical Ind., Co., Ltd), Eudragit RS100 (Röhm Pharma), ethylcellulose (EC, 100 cps; Wako Pure Chemical Industry, Osaka) and microcrystalline cellulose (Avicel® PH101, Shin-Etsu Chemical Ind., Co., Ltd) were used. Lidocaine (Xylocaine® injection, Fujisawa Pharmaceutical Co., Ltd) was employed as an internal standard for HPLC. All other chemicals were reagent grade.

Preparation of granules

Dipyridamole and polymers were dissolved in ethanol-dichloromethane (1 : 1) in a jacketed beaker connected to a thermostated water bath. A slurry of the appropriate stiffness was obtained by evaporating the solvent while maintaining the

water bath at 50°C. The slurry was forced through a 20-mesh sieve. The resultant materials clung to the sieve surface even after passing through the pore. After drying the initial mass at 50°C, the materials were scraped off with a spatula. A fraction of granules of size between 16- and 20-mesh was obtained.

A pH-dependent sustained-release granule preparation was formulated as follows. Dipyridamole and EC were dissolved in ethanol-dichloromethane (1 : 1), followed by the addition of Avicel with agitation by a magnetic stirring bar in a jacketed beaker connected to a thermostated water bath. The subsequent procedure was the same as described above.

Solubility studies

The solubility of dipyridamole was determined in solutions of various pH values at 37°C. The drug concentration in the equilibrated solution was determined spectrophotometrically against a blank at 285 nm after filtration through a 0.45 μm membrane filter (Toyo Roshi Co., Tokyo) and appropriate dilution with the same buffer solution.

In vitro release studies

The paddle method described in JP-XI was employed for evaluation of the rates of release of dipyridamole from preparations. The release vessel in a constant temperature water bath was cylindrical in shape. The paddle was assembled at a depth of 25 ± 2 mm from the bottom. Each preparation containing 2 mg of dipyridamole was dispersed in 500 ml of the following media of various pH values: pH 1.2 (No. 1 for disintegration test, JP-XI), pH 3 (0.1 M CH_3COONa-0.1 N HCl), pH 4 (0.1 M CH_3COONa-0.1 M CH_3COOH), pH 5 (0.1 M CH_3COONa-0.1 M CH_3COOH), pH 6 (0.05 M Na_2HPO_4-0.05 M KH_2PO_4), and pH 7 (0.05 M Na_2HPO_4-0.05 M KH_2PO_4) at 37 ± 0.5°C. The ionic strength of each medium was adjusted to 0.1 M by addition of NaCl. Two kinds of release tests were performed. Release profiles were examined in the same buffer solutions at all times. Another test involved changing the medium at 2 h. Namely, the preparation was transferred from pH 1.2 buffer solution to pH 6.0 or 7.0 buffer solution at 2 h. The shaft of the paddle was rotated at 150 rpm. 5 ml samples were removed at predetermined intervals and filtered through the membrane filters of pore size 0.45 μm (Toyo Roshi Co., Tokyo). Immediately following, 5 ml of fresh medium was added to the dissolution vessel in order to maintain the original volume. The solutions were analyzed spectrophotometrically against a blank at 285 nm. Triplicate runs were made on each study.

Oral administration of dipyridamole preparations to rabbits

The gastric acidity of white male rabbits (2.5–3.0 kg) was controlled according to the method of Takahashi et al. (1983). Sustained-release granules or a commercial powder containing dipyridamole of 4 mg/kg weight in hard gelatin capsules (JP-XI, No. 3) was administered to the gastric-acidity-controlled rabbits 10 min after feeding.

Each preparation was administered into the stomach of the rabbit via a plastic catheter attached to a syringe. The plastic catheter was threaded through a hole in a wooden stick holding the mouth open, and into the stomach. The capsule was pushed through to the open end of the plastic catheter with 20 ml of water. No water was given during the first 4 h and food was not allowed until the absorption study had been completed. About 2.5 ml of blood was drawn from the marginal ear vein before administration (time 0) and at 0.5, 1, 2, 3, 4, 6, 9 and 12 h post-dosing. Plasma samples were stored at -20°C for a few days until assaying the drug concentrations.

Oral administration of dipyridamole preparations to humans

Four healthy male subjects (age range 22–37 years) participated in the present study. A commercial powder and pH-independent sustained-release granules containing dipyridamole of 1 mg/kg weight in hard gelatin capsules (JP-XI, No. 1) were administered to the subjects with 100 ml water. The subjects fasted from 10 h before to 4 h after taking the drug. Blood samples (5 ml) were collected before administration (time 0) and

at 0.5, 1, 2, 4, 9 and 12 h post-dosing. Plasma samples were stored at −20°C for a few days prior to HPLC assay of drug concentrations.

Assay of dipyridamole in plasma

The HPLC method employed was that reported by Williams et al. (1981), as modified slightly. Dipyridamole was extracted with 5 ml of diethyl ether after adding 1 ml of 0.1 N sodium hydroxide and 1 ml of plasma. The mixture was shaken for 15 min and centrifuged at $1000 \times g$ for 5 min. 4 ml of the organic layer was removed and evaporated in vacuo. The residue was reconstituted with 100 μl of mobile phase containing an internal standard (lidocaine) and 20 μl of the solution then injected into the HPLC system. The HPLC conditions were as follows: pump and detector, Hitachi 635A type equipped with Hitachi 638-41 UV monitor (Tokyo, Japan); column, ERC-ODS-1161 (6 mm i.d. × 10 cm, particle size 3 μm; Erma Optical Works) warmed to 55°C using a constant-temperature water bath circulator; mobile phase, 0.01 M Na_2HPO_4-CH_3CN (1 : 1) adjusted to pH 8.0 by addition of phosphoric acid; flow rate, 1 ml/min; detection, at 280 nm.

Pharmacokinetic analysis and statistics

Plasma concentration was plotted vs time. The peak plasma concentration (C_{max}) and the time to peak plasma concentration (T_{max}) were determined directly from the graphs. The area under the plasma concentration-time curve from 0 to 12 h after administration ($AUC_{0-12\,h}$) was calculated according to the linear trapezoidal rule. The mean residence time (MRT) was evaluated from the following equation (Yamaoka et al., 1978):

$$MRT = \int_0^t tC\,dt \Big/ \int_0^t C\,dt$$

where C is the concentration of drug in the plasma at any time t.

Statistical differences between high and low gastric acidity groups after administration of three kinds of dipyridamole formulations were assessed using Student's t-test. A p value less than 0.05 was considered statistically significant.

Results and Discussion

The values obtained for the solubility of dipyridamole at various pH values are listed in Table 1. Equilibrated buffer solutions of pH < 3 resulted in a higher final pH as compared to the initial value. The solubility at pH 2.5 was about 6000-fold larger than that at pH 7. It was assumed that the dissolution of drug in the GI tract would be incomplete and that an unsatisfactory extent of absorption would result in cases where the gastric pH or gastric emptying rate increased after oral administration of dipyridamole.

The release profiles for dipyridamole commercial powder are shown in Fig. 1. Drug release was rapid below pH 4, while slower rates of release were observed with increasing pH.

For the sustained-release dipyridamole granule formulation prepared using the hydrophobic polymer EC as a granule binder, drug release from the granules was found to be dependent on the solubility of the drug at all pH values examined (Fig. 2). It was also assumed that an increase in gastric pH or gastric emptying rate decreased the bioavailability of the granule preparation, since release of dipyridamole was almost negligible above pH 5 (Fig. 2).

Hasegawa et al. (1985a–c, 1986) prepared coevaporates of various drugs using enteric coating polymers as carriers of the solid dispersion. The dissolution profiles of the solid dispersions

TABLE 1

Solubility of dipyridamole at 37°C

pH		Solubility (μg/ml)
Initial	Final	
1.2	2.5	29920
3.0	3.4	1780
4.0	4.0	542
5.0	5.0	60
6.0	6.0	13
7.0	7.0	5

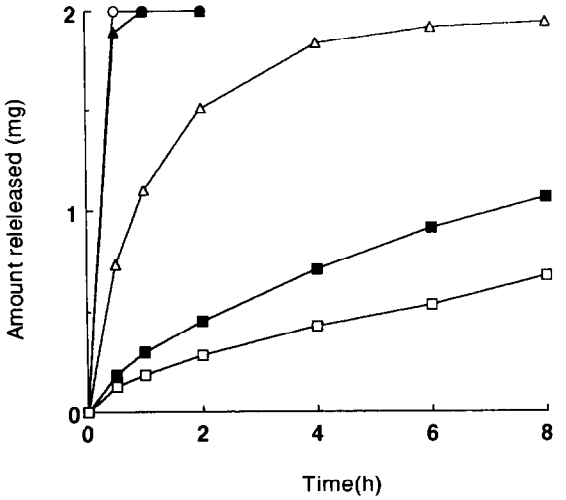

Fig. 1. Release profiles of commercial powder in media of various pH: (●) pH 1.2; (○) pH 3; (▲) pH 4; (△) pH 5; (■) pH 6; (□) pH 7.

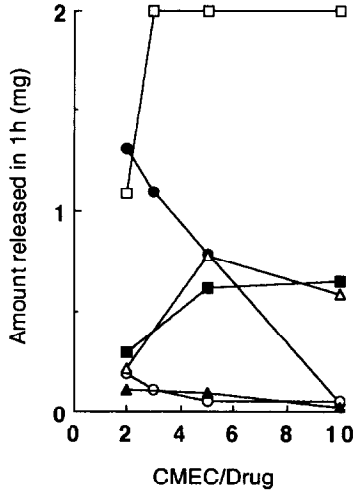

Fig. 3. Relationship of the ratio of CMEC to dipyridamole and amount released within 1 h at various pH values. Symbols as in Fig. 1.

demonstrated the occurrence of supersaturation at neutral pH and the absence of dissolution at acidic pH. Several recently reported investigations describe the use of water-insoluble polymers as carriers in solid dispersions for reducing the rate of release from the preparations (Kohri, 1989; Oth and Möes, 1989; Michelle et al., 1990). We attempted to prepare sustained-release granules showing pH-independent release by using the above-mentioned techniques. Firstly, the enteric coating polymer, CMEC, was used to enhance the release rate above pH 5. As shown in Fig. 3, the amount released during a period of 1 h was enhanced above pH 5, whereas below pH 4 a reduction in the amount released was observed with increasing CMEC.

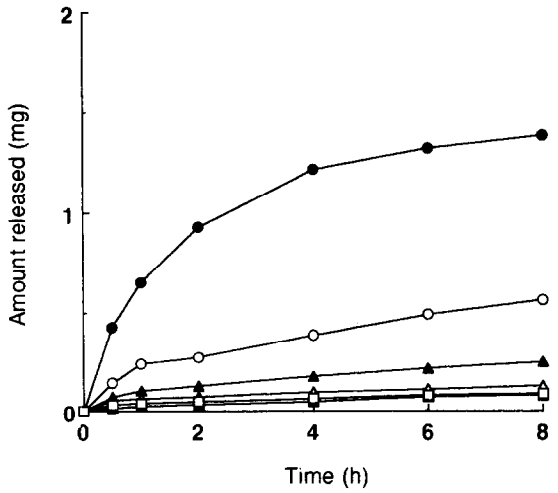

Fig. 2. Release profiles of pH-dependent sustained-release granules composed of dipyridamole-EC-Avicel (1:5:4) in media of various pH. Symbols are the same as in Fig. 1.

Although any ratio of CMEC to drug can be used, in the present study we chose to examine a ratio of 5. Incorporation of TC-5 (1.0 g) into the mixture of CMEC (1.0 g) and drug (0.2 g) increased the rate of release below pH 4 (Fig. 4). The drug is considered to interact with CMEC or TC-5 in the granule preparation. The rate of release of drug in the interaction with CMEC should result in an identical pattern to that in Fig. 3 whereas the corresponding situation for TC-5 should give rise to the rapid release of drug, the rate being dependent on the solubility at each pH value. Consequently, the rates of release appeared to improve at all pH values (Fig. 4).

Furthermore, the hydrophobic polymer, Eudragit RS100, was incorporated in order to retard the release rates at all pH values. pH-independent release was observed from the granule preparation composed of CMEC, TC-5 and Eudragit RS100 at ratios vs the drug of 5, 5 and 15,

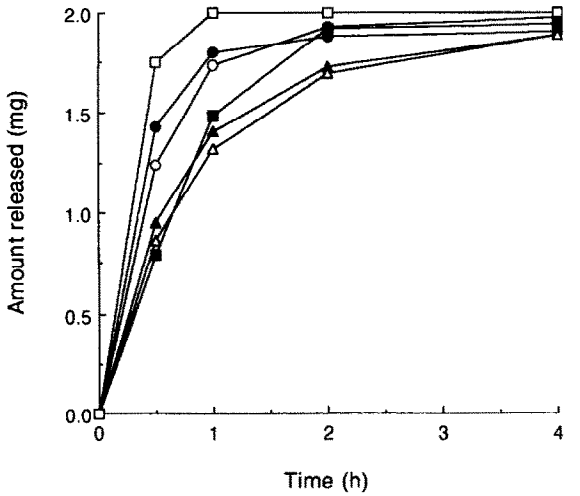

Fig. 4. Release profiles of the granules composed of dipyridamole-CMEC-TC-5 (1:5:5) in media at various pH values. Symbols as in Fig. 1.

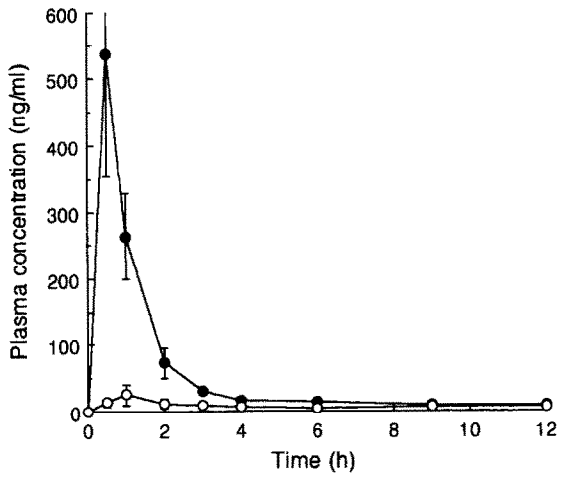

Fig. 6. Plasma dipyridamole concentrations after oral administration of commercial powder to high (●) and low (○) acidity groups. Results are means ± S.E. ($n = 5$).

respectively (Fig. 5a). The rate of release from this type of pH-independent sustained-release granules was also found to be unaffected by changes in the pH of the medium from 1.2 to 6.0 or 7.0 (Fig. 5b).

Drug release from such matrices below pH 4 should be improved by dissolving TC-5 and suppressed by CMEC and Eudragit RS100, while that above pH 5 should be enhanced by dissolving TC-5 and CMEC and suppressed by Eudragit RS100.

The possibility exists that the changes in bioavailability of a drug in an oral dosage form, which exhibits in vitro pH-dependent dissolution characteristics, may be the result of variations in gastric pH (Ogata et al., 1986; Kohri et al., 1989). We used gastric-acidity-controlled rabbits as a model animal to assess the effect of gastric acidity on drug absorption, as reported previously (Kohri et al., 1989). In the present paper, three dipyridamole dosage forms, i.e., the commercial powder, and pH-dependent and pH-independent sustained-release granules, were administered orally to gastric-acidity-controlled rabbits.

Fig. 6 depicts the plasma concentration-time curves of dipyridamole following oral administration of the commercial powder to high and low

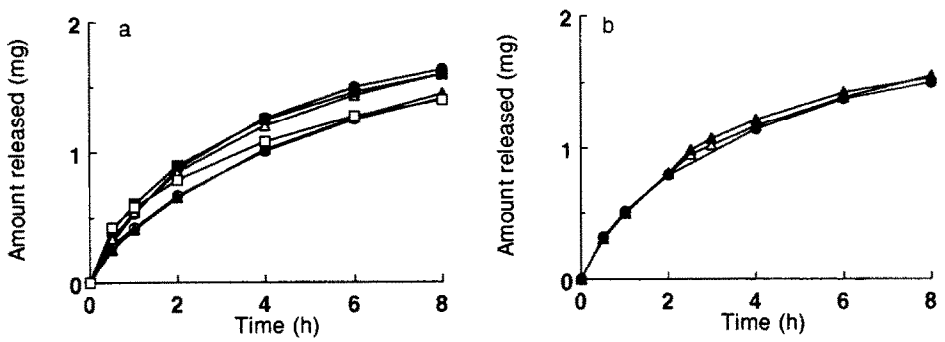

Fig. 5. Release profiles of pH-independent sustained-release granules composed of dipyridamole-CMEC-TC-5-Eudragit RS100 (1:5:5:15). (a) In media at various pH values. Symbols as in Fig. 1. (b) At pH 1.2 (●), and on changing pH of medium from pH 1.2 to 6 (△) and from pH 1.2 to 7 (▲) at 2 h.

TABLE 2

Effect of gastric acidity on pharmacokinetic parameters of dipyridamole after oral administration of commercial powder

Parameter	Gastric acidity	
	High	Low
C_{max} (ng/ml)	545.7 ± 159.6	26.4 ± 14.5 [a]
T_{max} (h)	0.6 ± 0.1	1.7 ± 0.5 [b]
AUC_{0-12h} (ng h ml^{-1})	673.9 ± 140.4	106.6 ± 40.2 [a]
MRT (h)	2.0 ± 0.2	5.4 ± 0.6 [c]

Results are means ± S.E. ($n = 5$).
[a] Significant ($p < 0.002$).
[b] Significant ($p < 0.005$).
[c] Significant ($p < 0.001$).

gastric-acidity-controlled rabbits while Table 2 lists the values of C_{max}, T_{max}, AUC_{0-12h} and MRT for both groups. The bioavailability for the high acidity group is clearly very much greater than that of the low acidity group. The C_{max} and AUC_{0-12h} values for the high acidity group are about 6- and 20-fold greater as compared to the low acidity group, respectively. Statistically significant differences exist in C_{max} and AUC_{0-12h} between the two groups (C_{max}, $p < 0.002$; AUC_{0-12h}, $p < 0.002$). T_{max} and MRT in the high acidity group are significantly shorter vs the low acidity group (T_{max}, $p < 0.005$; MRT, $p < 0.001$). The considerable extent of interindividual differences in bioavailability after oral administration of the commercial formulation of dipyridamole to human subjects reported by Arafat et al. (1989) may be ascribed to variations in gastric acidity or gastric residence time.

Fig. 7 illustrates the results obtained on pH-dependent sustained-release granules, the pharmacokinetic parameters being summarized in Table 3. Plasma concentrations for the high acidity group are evidently much higher than those for the low acidity group. C_{max} and AUC_{0-12h} in the high acidity group are significantly greater vs the low acidity group (C_{max}, $p < 0.05$; AUC_{0-12h}, $p < 0.005$), while MRT and T_{max} showed no statistically significant difference between the two groups. These data, obtained using the commercial powder and the pH-dependent sustained-release granule formulation, correlate closely with the results of solubility and release studies. It has been reported elsewhere that the release profiles of commercial sustained-release formulations vary at different pH values (Serajuddin and Rosoff, 1984; Yamada et al., 1990; Li Wan Po et al., 1991). That the bioavailabilities after oral administration of such sustained-release formulations might be affected by gastric acidity cannot be excluded as a possibility.

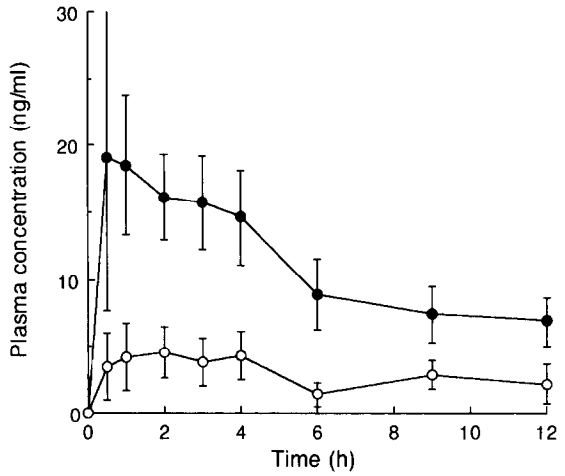

Fig. 7. Plasma dipyridamole concentrations after oral administration of pH-dependent sustained-release granules to high (●) and low (○) acidity groups. Results are means ± S.E. ($n = 4$).

Fig. 8 shows plasma concentration-time curves following oral administration of pH-independent sustained-release granules. The variability in plasma concentrations between both high and low acidity groups is seen to be markedly reduced

TABLE 3

Effect of gastric acidity on pharmacokinetic parameters of dipyridamole after oral administration of pH-dependent sustained-release granules

Parameter	Gastric acidity	
	High	Low
C_{max} (ng/ml)	28.2 ± 8.8	6.8 ± 1.6 [a]
T_{max} (h)	1.6 ± 0.8	2.4 ± 0.7
AUC_{0-12h} (ng h ml^{-1})	131.7 ± 16.2	35.2 ± 11.0 [b]
MRT (h)	4.8 ± 0.5	5.7 ± 1.2

Results are means ± S.E. ($n = 4$).
[a] Significant ($p < 0.05$).
[b] Significant ($p < 0.005$).

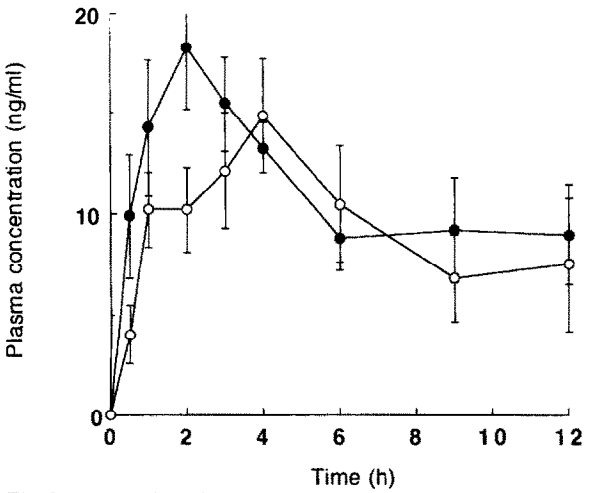

Fig. 8. Plasma dipyridamole concentrations after oral administration of pH-independent sustained-release granules to high (●) and low (○) acidity groups. Results are means ± S.E. ($n = 5$).

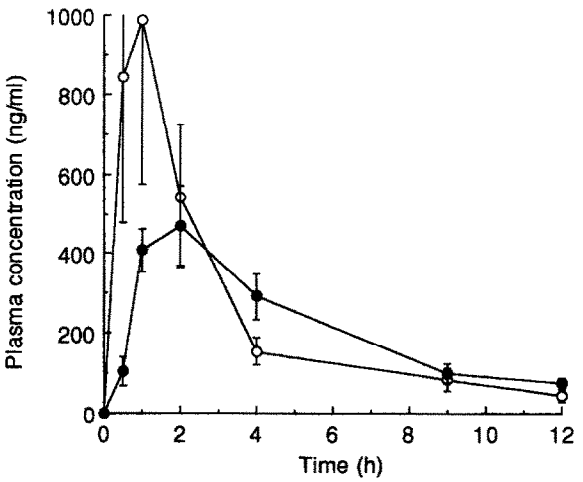

Fig. 9. Plasma dipyridamole concentrations after oral administration of pH-independent sustained-release granules (●) and commercial powder (○) to normal subjects. Results are means ± S.E. ($n = 4$).

by administration of this formulation. No statistically significant differences exist in the C_{max}, T_{max}, AUC_{0-12h} and MRT values between both groups (Table 4). These data demonstrate a close correspondence with the results of the release studies (Fig. 5).

The bioavailability of pH-independent sustained-release granules was observed to be greater as compared to those of the commercial powder and the pH-dependent sustained-release granule formulation after oral administration to the low acidity group (Tables 2–4). The MRT of the commercial powder in the low acidity group is also comparable to those of both types of sustained-release granules in both acidity groups (Tables 2–4). These results also correlate closely to those of the release studies.

However, for the pH-independent sustained-release granules, the bioavailability was less than that of the commercial powder on administration to the high acidity group. This discrepancy might result from the bile having a very high capacity for concentrating dipyridamole and its glucuronides following oral administration of the drug to rabbits (Zak et al., 1963). This pH-independent sustained-release granule preparation and the commercial powder were subsequently administered to human subjects. As shown in Fig. 9 and Table 5, C_{max} for the granule formulation fell to 50% of that for the commercial powder, although significant differences in C_{max} between the two preparations did not occur due to the large interindividual variability of the commercial powder. The low value of C_{max} for the granule preparation was an effective means of avoiding the side effect of headaches in all subjects. The plasma levels after oral administration of the granules were maintained for a greater duration of time as compared to those of the commercial powder. AUC_{0-12h} for the granule preparation was about 90% of that for the commercial powder. There were no statistically significant differ-

TABLE 4

Effect of gastric acidity on pharmacokinetic parameters of dipyridamole after oral administration of pH-independent sustained-release granules

Parameter	Gastric acidity	
	High	Low
C_{max} (ng/ml)	18.4 ± 0.2	16.3 ± 1.9
T_{max} (h)	1.8 ± 0.2	2.6 ± 0.6
AUC_{0-12h} (ng h ml^{-1})	132.6 ± 15.4	112.3 ± 16.5
MRT (h)	5.3 ± 0.5	5.5 ± 0.4

Results are means ± S.E. ($n = 5$).

TABLE 5

Pharmacokinetic parameters of dipyridamole after oral administration of commercial powder and pH-independent sustained-release granules to human subjects

Parameter	Commercial powder	pH-independent sustained-release granules
C_{max} (ng/ml)	1040.9 ± 386.3	481.3 ± 183.5
T_{max} (h)	1.1 ± 0.3	1.5 ± 0.3
AUC_{0-24h} (ng h ml^{-1})	2920.5 ± 952.0	2593.3 ± 460.3

Values are means ± S.E. ($n = 4$).

ences in AUC_{0-12h} and T_{max} between both preparations. Thus, this granule preparation represents a sustained-release dosage form which has a good bioavailability in human subjects.

As a consequence of our investigation, the use of pH-independent sustained-release granules could reduce variability in the extent of drug absorption. In designing sustained-release dosage forms, it is necessary to develop pharmaceutical preparations whose bioavailability remains unaffected by changes in gastric acidity. In conclusion, the preparation of pH-independent sustained-release granules could be a useful approach to formulating sustained-release dosage forms that potentially reduce intra- and interindividual variabilities in drug absorption.

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