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Application of Solid Dispersions with Enteric Coating Agents to Overcome Some Pharmaceutical Problems

AKIHIKO HASEGAWA,* RIE KAWAMURA, HIROSHI NAKAGAWA, and ISAO SUGIMOTO

Pharmaceuticals Research Center, Kanebo, Ltd., 1–5–90, Tomobuchi-cho, Miyakojima-ku, Osaka 534, Japan

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A solid dispersion technique with enteric coating agents was applied to two drugs which present some pharmaceutical problems. The first drug, digoxin, is poorly water-soluble and chemically unstable in an acidic medium. The solid dispersions suppressed the dissolution rate of the drug in JP X 1st fluid (JP disintegration medium, pH 1.2), and improved the chemical stability. In JP X 2nd fluid (JP disintegration medium, pH 6.8), the solid dispersions showed rapid dissolution and supersaturation. It was concluded that this technique can provide an effective dosage form of digoxin for gastrointestinal absorption. The second drug, dipyridamole, is a poorly water-soluble organic base. The solid dispersion technique was applied to prepare a delayed absorption dosage form with good bioavailability. The solid dispersions showed suppressed a dissolution in an acidic medium, and gave supersaturation in a neutral or alkaline medium. Oral administration of this dosage form resulted in delayed absorption with good bioavailability.

Keywords——solid dispersion; enteric coating agent; digoxin; dipyridamole; acid degradation; sustained-release dosage form

The solid dispersion technique was originally used to enhance the dissolution rate of poorly water-soluble drugs by using a water-soluble inert carrier such as polyvinylpyrrolidone or polyethylene glycol.[1] We attempted to apply a solid dispersion technique using different types of enteric coating agents as inert carriers to control the release rate of water-insoluble and short-acting drugs, and reported the physicochemical properties[2,3] and bioavailability[4] of solid dispersions obtained from nifedipine and enteric coating agents. Some physical properties of solid dispersions of other water-insoluble drugs were also reported.[5] Most of the drugs in these solid dispersions were amorphous, and the dissolution of the solid dispersions was practically nil in JP X 1st fluid (JP disintegration medium, pH 1.2). However, they dissolved rapidly in JP X 2nd fluid (JP disintegration medium, pH 6.8) and showed supersaturation phenomena.[2,5] This new dosage form provided delayed absorption of nifedipine with good bioavailability when given by oral administration, so the technique was applied to develop a sustained-release preparation of nifedipine.[6]

In this work, the solid dispersion technique was first applied to digoxin to overcome the problems of degradation in the stomach and poor dissolution. The technique was also applied to dipyridamole, which is soluble in acidic media and practically insoluble in neutral and alkaline media, to prepare a sustained-release dosage form with good bioavailability.

Experimental

Materials——Digoxin (Boehringer Mannheim GmbH) and dipyridamole (Shizuoka Caffeine Co., Ltd.) were used as received. The particle sizes determined by an air permeability method were approximately 2 and 12 μm, respectively. Hydroxypropylmethylcellulose phthalate 200731 (HP-55, JP X grade, Shin-Etsu Chemical Ind., Co., Ltd.), methacrylic acid–methacrylic acid methyl ester copolymer (Eudragit L and S, Röhm Pharma GmbH, W.

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Germany), and carboxymethylethylcellulose (CMEC, Freund Ind., Co., Ltd.) were also used as received. Sucrose (Non Pareil 103, Freund Ind., Co., Ltd.) was used as an inert core material. Plain tablets containing 0.25 mg of digoxin (Digoxin-Sandoz®, Sankyo Co., Ltd.) and 25 mg of dipyridamole (Persantin®, Nippon Boehringer Ingelheim Co., Ltd.) were obtained commercially. Other chemicals were of reagent grade or JP X grade.

Preparation of Solid Dispersions——A drug (3 g) and a polymer (9—30 g) were dissolved in 90—300 ml of mixed solvent (ethanol–dichloromethane (1 : 1)) and then the solvent was evaporated off under reduced pressure. The residual solid was pulverized and the 32—80 mesh fraction was used in the dissolution study.

X-Ray Diffraction Study——The X-ray diffraction patterns were determined with an X-ray diffractometer (Geigerflex 2027, Rigaku Denki, Ltd.; Cu $K\alpha$; 30—40 kV; 10—20 mA).

Dissolution Study——i) Digoxin: A simple beaker-stirrer dissolution method as reported in the previous paper[3] was employed. The test solution was analyzed by the high performance liquid chromatography (HPLC) method.[7]

ii) Dipyridamole: The pH shift method[8] was modified and used. The dissolution test apparatus as reported in the previous paper[3] was used. The initial dissolution medium (500 ml, 37°C) was JP X 1st fluid, the pH of which was preadjusted to 2 with 0.5 M KH_2PO_4–NaOH buffer (pH 12). A sample equivalent to 100 mg of dipyridamole was placed in the dissolution medium, 10 ml of the test solution was taken every 15 min and the pH of the solution was checked. Then, 10 ml of 0.5 M KH_2PO_4–NaOH buffer (pH 12) was added to the dissolution medium. The test solution was filtered (Millipore, 0.22 μm pore size) and assayed spectrophotometrically at 293 nm.

All dissolution experiments were carried out in duplicate and the results were highly reproducible. Thus, only mean values are reported.

Preparation of Granules——i) Granules Coated with Solid Dispersions: Granules whose surface was coated with solid dispersion were prepared by the method reported in the previous paper.[6]

ii) Control Granules: In the case of dipyridamole, a conventional enteric-coated dosage form was prepared as a control for the administration study by using a CF granulator (model CF 360, Freund Ind., Co., Ltd.). Non Pareil 103 (1000 g) was coated with a mixed powder of 100 g of dipyridamole and 100 g of lactose using an aqueous solution of hydroxypropylcellulose as a binder. Then, Eudragit S solution was spray-coated on the surface of the granules containing dipyridamole. The control granules did not disintegrate and dipyridamole did not dissolve in JP X 1st fluid, but the test granules disintegrated within 30 min in pH 7.5 phosphate buffer.

Absorption Behavior in Beagle Dogs——Male beagle dogs (11—13 kg), which had been fasted for 24 h but allowed free access to water, were orally given test preparations with 80 ml of water. Doses were administered by the cross-over arrangement with an interval of one week.

i) Digoxin: A sample equivalent to 0.25 mg of digoxin was administered. Plasma samples were assayed for digoxin by using an enzyme immunoassay procedure (Merkit® Digoxin, Dainippon Pharmaceutical Co., Ltd.).

ii) Dipyridamole: A sample equivalent to 50 mg of dipyridamole was administered. The plasma level of dipyridamole was assayed by the HPLC method.[9]

Results and Discussion

I. Digoxin Solid Dispersions

The glycosidic nature of the digoxin molecule makes it susceptible to hydrolysis in an acidic environment, the degradation rate being inversely proportional to pH.[10] Digoxin degradation is closely related to reduced cardiac activity, since the main hydrolysis product is digoxigenin[11] and this product possesses only about one-tenth the cardioactivity of the parent glycoside.[12] Clark and Kalman[13] found digoxin degradation products in the urine of patients. The studies of Gault *et al.*,[14] who observed intragastric hydrolysis of digoxin at maximum acid secretion induced by pentagastrin infusion, have demonstrated the possibility of degradation of orally administered digoxin by acid hydrolysis in the stomach prior to absorption. Thus, it is not desirable to have rapid digoxin dissolution in the stomach of a patient, because a significant portion of the drug will be degraded. Digoxin was used as a model drug unstable in an acidic medium in this work, and the dissolution and absorption characteristics of the enteric solid dispersion were investigated.

(1) X-Ray Diffraction Pattern——Figure 1 shows the X-ray diffraction patterns of the solid dispersions.

HP-55 and Eudragit L were used as carriers of the solid dispersions. The peaks attributable to digoxin crystals were observed in both (1 : 3) solid dispersions. However, digoxin was present in its amorphous form in (1 : 10) solid dispersions.

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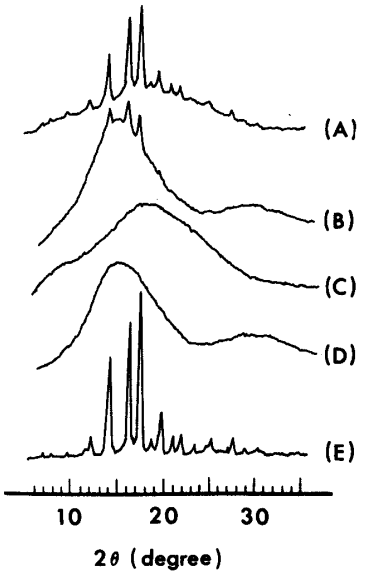

Fig. 1. X-Ray Diffraction Spectra of Digoxin Solid Dispersions

(A), digoxin–HP-55 (1 : 3); (B), digoxin–Eudragit L (1 : 3); (C), digoxin–HP-55 (1 : 10); (D), digoxin–Eudragit L (1 : 10); (E), digoxin crystals.

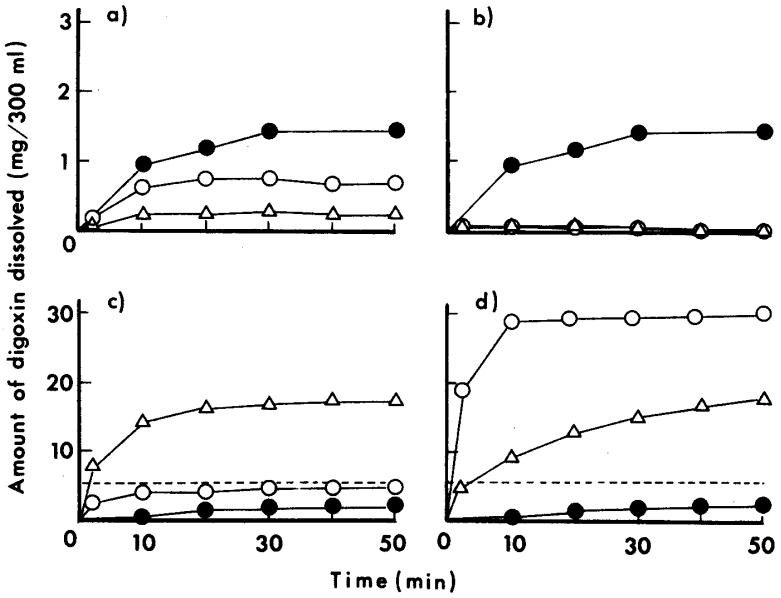

Fig. 2. Dissolution Behavior of Digoxin from Solid Dispersions in JP X 1st Fluid (a, b) and 2nd Fluid (c, d)

a, c) (1 : 3) solid dispersions. b, d) (1 : 10) solid dispersions.
(○), HP-55; (△), Eudragit L; (●), digoxin crystals.
A sample equivalent to 30 mg of digoxin was added to 300 ml of dissolution medium. The dotted line shows the solubility of digoxin in JP X 2nd fluid.

(2) Dissolution Behavior——Figure 2 shows the dissolution properties of digoxin from the solid dispersions in JP X 1st and 2nd fluids. All of the solid dispersions suppressed the dissolution rate of digoxin compared with that of digoxin crystals in JP X 1st fluid, and digoxin dissolution from (1 : 10) solid dispersions was practically nil. On the other hand, the amorphous (1 : 10) solid dispersions showed rapid dissolution and supersaturation in JP X 2nd fluid, while digoxin crystals dissolved very slowly. Eudragit L (1 : 3) solid dispersion also showed supersaturation in JP X 2nd fluid. This may be due to the low degree of crystallinity of the drug,[5] since the X-ray diffraction peaks were small.

No decrease in the amount of drug in solution was observed at pH 1.2, indicating that little degradation of digoxin occurred. However, peaks thought to be due to degradation

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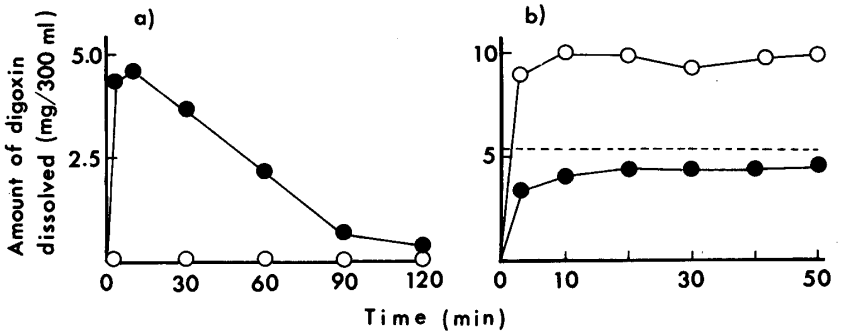

Fig. 3. Dissolution Behavior of Digoxin from Plain Tablet and Granules Coated with Solid Dispersion (Digoxin–HP-55 (1 : 10)) in JP X 1st Fluid (a) and 2nd Fluid (b)

(○), granules; (●), plain tablet.
A sample equivalent to 10 mg of digoxin was added to 300 ml of dissolution medium. The dotted line shows the solubility of digoxin in JP X 2nd fluid.

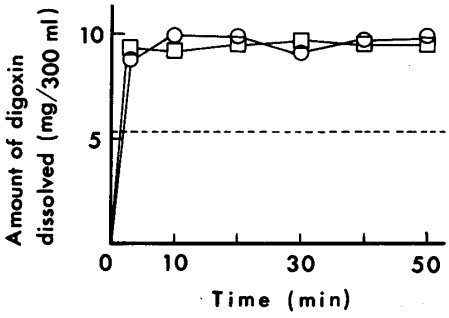

Fig. 4. Dissolution Behavior of Digoxin from Granules Coated with Solid Dispersion (Digoxin–HP-55 (1 : 10)) in JP X 2nd Fluid after Pretreatment with JP X 1st Fluid for 2 h

(○), untreated; (□), pretreated with JP X 1st fluid.
A sample equivalent to 10 mg of digoxin was added to 300 ml of JP X 2nd fluid. The dotted line shows the solubility of digoxin.

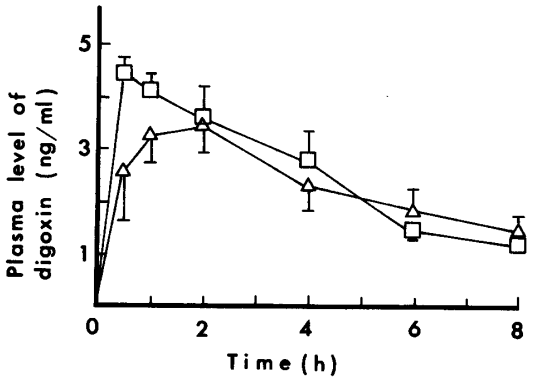

Fig. 5. Comparison of Mean Plasma Digoxin Levels after Oral Administration of Plain Tablet and Granules Coated with Solid Dispersion (Digoxin–HP-55 (1 : 10)) to Beagle Dogs (Equivalent 0.25 mg of Digoxin)

(△), granules; (□), plain tablet.
Each point represents the average ± S.E. of four determinations.

products of digoxin[7] were apparent in a liquid chromatogram. Under these experimental conditions, it seems that digoxin molecules in solution were degraded, but the large amount of the solid drug available is expected to compensate for the resulting decrease in the amount of digoxin in solution. Granules whose surface was coated with digoxin–HP-55 (1 : 10) solid dispersion were prepared for dissolution and absorption studies. Figure 3 shows the dissolution properties of digoxin from the granules and from plain tablets in JP X 1st and 2nd fluids.

The amount of digoxin in solution was decreased due to the degradation of digoxin molecules following rapid dissolution in the case of the plain tablet in JP X 1st fluid. This is consistent with data on the stability of digoxin.[10] The dissolution of digoxin from the granules was practically nil in JP X 1st fluid. In JP X 2nd fluid, however, the granules showed very rapid and complete dissolution, and supersaturation. Digoxin from the plain tablets rapidly dissolved in JP X 2nd fluid, but supersaturation was not observed.

Figure 4 shows the dissolution properties of digoxin from the ganules in JP X 2nd fluid after pretreatment with JP X 1st fluid for 2 h.

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The dissolution in JP X 2nd fluid was not affected by the pretreatment with JP X 1st fluid. It was confirmed that the degradation of digoxin in the solid dosage form was negligible. The ploblems of acid hydrolysis and poor dissolution of digoxin in the gastrointestinal tract might therefore be overcome by the application of this solid dispersion technique to the dosage form.

(3) Absorption in Beagle Dogs——Figure 5 shows the mean plasma concentration of digoxin after oral administration of granules coated with digoxin–HP-55 (1 : 10) solid dispersion and plain tablets (equivalent to 0.25 mg of digoxin) to four beagle dogs.

Digoxin from the plain tablet was rapidly absorbed compared to that from the granules. As the granules were entero-soluble, the absorption of digoxin was delayed. Mean area under the blood concentration–time (0—8 h) curve ($AUC_{0-8\,h}$) values were 20.6 ± 3.1 and 18.6 ± 4.7 ng·h/ml for the plain tablet and the granules, respectively. These $AUC_{0-8\,h}$ values are not statistically significantly different, though the $AUC_{0-8\,h}$ value of the plain tablet might be expected to be lower than that of the granules because of the rapid degradation of digoxin in JP X 1st fluid in the case of the plain tablet (Fig. 3). In this work, an enzyme immunoassay procedure (Markit® Digoxin) was used for the determination of the plasma level of digoxin, since the HPLC method could not be used because of its low sensitivity. Unfortunately, immunoassay procedures currently available to determine digoxin concentration in plasma can not distinguish between digoxin and its degradation products. Thus, the amount of digoxin absorbed from the granules might be higher than that from the plain tablet.

Enteric coating may be useful for improving the chemical stability of digoxin in acidic medium. However, Flasch *et al.*[15] reported that the bioavailability of the enteric-coated preparation was lower than that of a plain formulation, using digoxin as a model drug. In this study, the $AUC_{0-8\,h}$ value of the granules was similar to that of the plain tablet. This is an important characteristic of the solid dispersion technique. From these results, it is concluded that this special physicochemical drug modification may make it possible to administer the drug orally in a form which is readily available for gastrointestinal absorption.

II. Dipyridamole Solid Dispersions

The solubility of a poorly water-soluble organic base may vary greatly in the gastrointestinal pH range, depending on the solubility of the ionized and un-ionized forms or the pK_a of the compound. These drugs may show irregular and imcomplete absorption from the gastrointestinal tract, since the drug solubility is affected by the gastric acidity. Further, it seems to be difficult to prepare a sustained-release dosage form of a basic drug with good availability by conventional methods, because the dissolution rate or solubility decreases remarkably when the dosage form reaches the small intestine.[16] Ogata *et al.*[17] developed a new peroral test agent, GA-Test, containing riboflavin granules coated with polyvinylacetal diethylaminoacetate for assessing gastric acidity, and they found that the probability of subjects having low acidity appeared to increase with increasing age. They also reported[18] that the acidity of gastric fluid affects the bioavailability of orally administered drugs whose dosage forms show pH-dependent drug release. The pH dependency may arise from the physicochemical properties of the drug itself or the pH-dependent dissolution properties of the coating material. For example, the bioavailability of a poorly water-soluble organic base such as cinnarizine is extremely low in subjects having low acidity compared to subjects having high acidity.[19] Solid dispersions of poorly water-soluble organic bases with enteric coating agents may improve the drug dissolution in the small intestine and should be suitable for developing delayed absorption dosage forms with good bioavailability. Further, the bioavailability would not be affected by the gastric acidity. In order to evaluate the physicochemical and absorption properties of solid dispersions of poorly water-soluble organic bases, dipyridamole was used as a model drug in this paper.

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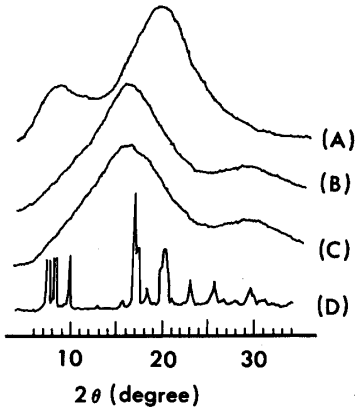

Fig. 6. X-Ray Diffraction Spectra of Dipyridamole Solid Dispersions (Dipyridamole–Polymer (1 : 3))

(A), CMEC; (B), Eudragit L; (C), Eudragit S; (D), drug crystals.

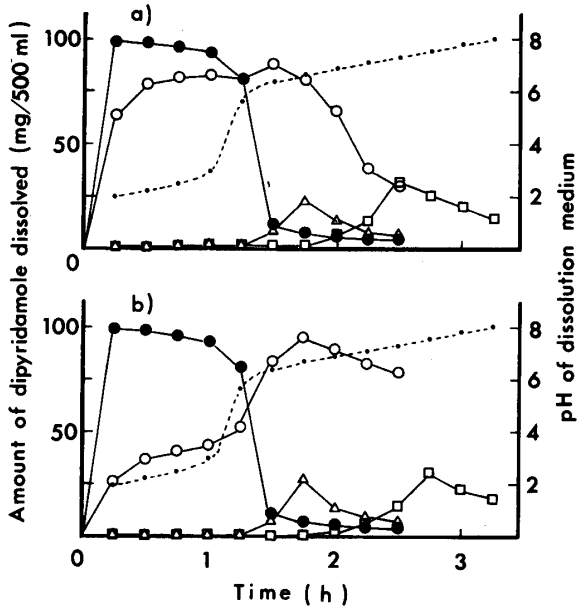

Fig. 7. Dissolution Behavior of Dipyridamole from Solid Dispersions and pH Change (------) of the Dissolution Medium in the pH Shift Dissolution Test Method

a) (1 : 3) solid dispersions. b) (1 : 6) solid dispersions. (○), CMEC; (△), Eudragit L; (□), Eudragit S; (●), dipyridamole crystals.

A sample equivalent to 100 mg of dipyridamole was added to 500 ml of dissolution medium.

(1) X-Ray Diffraction Pattern——Figure 6 shows the X-ray diffraction patterns of the solid dispersions.

CMEC, Eudragit L and Eudragit S were used as carriers. Dipyridamole was present in its amorphous form in all (1 : 3) solid dispersions.

(2) Dissolution Properties——In order to evaluate the dissolution properties of the drug crystals and the solid dispersions, the pH shift method[8] which simulates the pH change at the surface of the samples after oral administration was used. The polymers used as carriers were CMEC, Eudragit L and Eudragit S. They are soluble above pH 5.5, 6.0 and 7.0, respectively. As the phthalate groups of the polymer disturbed the drug analysis by the ultraviolet method, HP-55 or CAP was not studied as a carrier of the solid dispersions in this study. Figure 7 shows the dissolution properties of dipyridamole crystals and the solid dispersions in a medium whose pH was changed continuously from 2 to 8.

Dipyridamole crystals rapidly dissolved at the initial low pH stage, but the amount of drug dissolved decreased drastically at about pH 5. At the later stage, dipyridamole was practically insoluble. All of the solid dispersions suppressed the dissolution of dipyridamole at the initial low pH stage and improved the dissolution at neutral or alkaline pH. The amount of drug in solution increased remarkably at the polymer-dissolving pH. In the case of CMEC, the amount of polymer affected the dissolution rate of dipyridamole in acidic medium. That is, the dissolution rate was decreased as the amount of polymer increased. The dissolution of dipyridamole from Eudragit L or Eudragit S solid dispersions was practically nil in acidic medium.

(3) Absorption in Beagle Dogs——Granules whose surface was coated with solid dispersions (dipyridamole–Eudragit S (1 : 6)) were prepared for this absorption study. As Eudragit S dissolved above pH 7, this system is expected to be more effective for delayed

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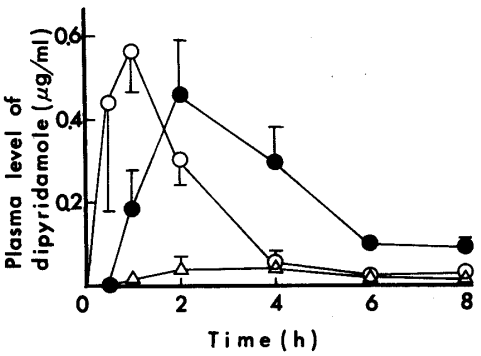

Fig. 8. Mean Plasma Concentration of Dipyridamole after Oral Administration of the Test Preparations (Equivalent to 50 mg of Dipyridamole) to Beagle Dogs

(●), granules coated with dipyridamole–Eudragit S (1 : 6) solid dispersion; (○), plain tablet; (△), conventional enteric dosage form.

Each point represents the average ± S.E. of four determinations.

TABLE I. Comparison of Bioavailability Parameters

Sample	T_{max} (h)	C_{max} (μg/ml)	AUC_{0-8h} (μg·h/ml)
Granules A[a]	2.5 ± 1.0	0.57 ± 0.10	1.67 ± 0.31
Granules B[b]	2.5 ± 1.7	0.06 ± 0.03	0.23 ± 0.21
Plain tablet[c]	0.7 ± 0.3	0.69 ± 0.29	1.34 ± 0.35

Each value represents the average ± S.D. *a*) Granules coated with dipyridamole and Eudragit S (1 : 6) solid dispersion. *b*) The surface of the granules containing dipyridamole was spray-coated with Eudragit S. *c*) Persantin®.

absorption than that based on CMEC or Eudragit L. The dissolution behavior of the granules was similar to that of the solid dispersion (Fig. 7). The absorption characteristics of dipyridamole after oral administration of the granules coated with dipyridamole–Eudragit S (1 : 6) solid dispersion to four beagle dogs are shown in Fig. 8 and Table I, together with the results for the plain tablet and the conventional enteric-coated dosage granules.

The dissolution behavior of the plain tablet was similar to that of dipyridamole crystals (Fig. 7). That is, the dissolution of dipyridamole was rapid at acidic pH and practically nil at neutral or alkaline pH. Rapid absorption and elimination of dipyridamole were observed following oral administration of the plain tablet. It was found that dipyridamole from the granules coated with Eudragit S solid dispersion was absorbed slowly. The AUC_{0-8h} value of the granules coated with Eudragit S solid dispersion was similar to that of the plain tablet. However, the conventional enteric-coated dosage form showed very poor absorption. The poor bioavailability of the conventional enteric-coated dosage form is due to the low solubility of dipyridamole in the small intestine. In the case of the granules coated with solid dispersion, suppression of dissolution in acidic medium and supersaturation in neutral or alkaline medium resulted in slow absorption with good bioavailability.

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