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Effect of adsorbents on the absorption of lansoprazole with surfactant

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Abstract

Lansoprazole (LPZ) is a representative drug that shows a high inter-subject variation of bioavailability (BA). Solid preparation composed of surfactant, adsorbent and LPZ were prepared to improve the dissolution and absorption of LPZ, and the BA of LPZ was measured in rats and dogs. As surfactant, Tween 80, polyoxy 60 hydrogenated caster oil derivative (HCO-60) and PEG-8 caprylic/capric glycerides (Labrasol) were used. As adsorbant, porous silicon dioxide (Sylysia 550, 320), magnesium aluminometa silicate (Neusilin S_2, NS_2N, US_2,) and porous calcium silicate (Florite RE) were used. After small intestinal administration of LPZ, 5.0 mg/kg, solution with HCO-60 showed the highest plasma LPZ concentration versus time curve of which C_{max} and AUC was 0.46 ± 0.01 μg/mL and 0.73 ± 0.03 μg h/mL. By comparing to that after i.v. injection of LPZ solution, 2.0 mg/kg, the BA of LPZ from HCO-60 solution was 39.0%, which was about seven times higher than that of LPZ powder. To solidify the LPZ solution with HCO-60, adsorbents were used and the obtained solid preparations were used for in vitro release experiment. Sylysia 320, Neusilin S_2 and Neusilin NS_2 showed the T50% of about 1 h. To evaluate the BA of these solid preparations, absorption study was performed in rats. Sylysia 550 system showed the higher AUC than other systems, showing the BA of 28.1%. Sylysia 550 system was filled in an enteric capsule and was orally administered to dogs and BA was compared with enteric tablet. The AUC of Sylysia 550 system was 2.16 ± 0.26 μg h/mL and was greater than enteric tablet and the BA of 71.7% was obtained. Solid system composed of LPZ, surfactant and adsorbent has suggested the possibility as a good tool to improve the BA of LPZ.

Keywords: Lansoprazole; Absorption; Bioavailability; Adosorbent; Surfactant; Oral administration

1. Introduction

Lansoprazole (LPZ) is a substituted benzimidazole and selectively inhibits the H^+/K^+-ATPase of the parietal cell of the stomach (Gerloff et al., 1996). The

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ATP-utilizing enzyme system localizes in the canalicular membrane of the stomach and is known to be the last step of the acid production in the stomach. LPZ is a representative proton pump inhibitor and has been clinically used in the therapy of gastric and duodenal ulcerative disease (Lew, 1999). Clinical studies performed to assess its clinical efficacy suggested the superiority or equivalence to H_2-receptor antagonist in gastric and duodenal ulcer, reflux esophagitis and Zollinger–Ellison syndrome (Stedman and Barclay, 1999). The clinical pharmacokinetic study performed by Gerloff et al. (1996) showed that the absolute bioavailability (BA) of LPZ was 91% for 30-mg capsule and 81% for 15-mg capsule. On the other hand, it was reported that CYP2C19 and 3A4 were involved in the metabolism of LPZ and wide inter-subject variation of LPZ systemic clearance was dependent on the genotype of CYP2C19 (Sohn et al., 1997; Pearce et al., 1996). However, the wide inter-subject variation of LPZ on its BA is not only ascribed to the genotype of the patients but also to the dissolution or absorption problem of LPZ. As LPZ is unstable in the stomach, i.e., gastric acid, enteric-coated granules are filled in a gelatin capsule. Kinoshita et al. (2002) suggests that the possibility of the degradation of LPZ by the gastric acid cannot be denied. In addition, LPZ is sparingly soluble in water. Therefore, even if LPZ is protected from the hydrolysis in the stomach, there is a possibility that LPZ is not well dissolved in the small intestine from which most drugs are absorbed into the systemic circulation.

We have been studying on the BA problem of water-insoluble drug like cyclosporin A and FK506, etc. (Takada et al., 1992, 1993; Katayama et al., 1995). To solve the BA problem of these super-lipophilic compounds, we used nonionic surfactant like polyoxy 60 hydrogenated caster oil derivative (HCO-60) and good BAs were obtained. Therefore, nonionic surfactants were used to accelerate the dissolution and improve the BA of LPZ. However, liquid formulation is not preferable as an oral formulation, because there is no capsule that can retain liquid formulation in itself without dissolution or degradation.

Solid dispersion is a pharmaceutical system for improving the solubility of poorly water-soluble drugs. In this system, the solubility of a drug is improved due to its amorphization. Currently, spray drying and layering on core particles are generally used to manufacture solid dispersions on a large scale (Kinoshita et al., 2002). However, these methods require a large amount of organic solvent to dissolve the drug and a hydrophilic polymer, which serves as the matrix in most cases. Organic solvents cause several problems including environmental pollution and toxicity due to the residual solvents. Therefore, adsorbents have been used to retain LPZ-surfactant mixture in an oral preparation. In this report, the system has been evaluated in in vivo absorption experiments using both rats and dogs.

2. Materials and methods

2.1. Materials

Lansoprazole (LPZ) was obtained from Sigma Chemicals (St. Louis, USA). Polysorbate 80 (Tween 80) and polyethylene glycol (PEG) 400 were obtained from Nacalai Tesque, Inc. (Kyoto, Japan). PEG-8 caprylic/capric glycerides (Labrasol) (Gattefösse, Lyon, France) was a gift from Chugai Boeki Co., Ltd. (Tokyo, Japan). Hydroxypropylmethyl cellulose phthalate (HP-55) was obtained from Shinetsu Chemicals, Inc. (Tokyo, Japan). Polyoxy 60 hydrogenated caster oil derivative (HCO-60) was obtained from Nikko Chemicals (Tokyo, Japan). Magnesium aluminometa silicates (Neusilin® US_2, S_2, N S_2N) were obtained from Fuji Chemical Industry Co., Ltd. (Toyama, Japan). Porous silicon dioxide (Sylysia® 550, 320) was obtained from Fuji Silysia Co., Ltd. (Aichi, Japan). Porous calcium silicate (Florite®RE) was obtained from Eisai Co., Ltd. (Tokyo, Japan). Dichloromethane, acetonitrile and ethanol were of HPLC grade. All other reagents were of analytical-reagent grade and were used as received. Male Wistar rats were obtained from SLC, Inc. (Hamamatsu, Japan) and standard solid meal of commercial food (Labo Diet®) was purchased from Nippon Nousan Co., Ltd. (Yokohama, Japan). Male beagle dogs (10.0–12.5 kg) used in this study and standard solid meal of commercial food (Labo D stock®) were obtained from Nippon Nousan Co., Ltd. (Yokohama, Japan).

2.2. Preparation

LPZ solution, 1.0 mg/mL, for i.v. study was prepared by dissolving LPZ with the mixture of PEG

Table 1
Composition of test oral LPZ preparations

Dosage form	Preparation code name	LPZ (mg)	Stabilizing agent (mg)	Surfactants			Adsorbent	
				Tween 80 (mg)	Labrasol (mg)	HCO-60 (mg)		
Powder	A	5	–	–	–	–	–	
Solution	B	5	5	170	–	–	–	
	C	5	5	–	170	–	–	
	D	5	5	–	–	170	–	
	E	5	5	–	–	60	–	
	F	5	5	–	10	60	–	
Solid	G	5	5	–	–	60	Sylysia 550	26 mg
	H	5	5	–	–	60	Sylysia 320	20 mg
	I	5	5	–	–	60	Neusilin S2	34 mg
	J	5	5	–	–	60	NeusilinNS2N	35 mg
	K	5	5	–	–	60	Neusilin US2	20 mg
	L	5	5	–	–	60	Florite RE	7.5 mg

Each value shows the formulated amount of LPZ and pharmaceutical additives for 1 kg of body weight of the experimental animals.

400 and 1/150 M NaOH (2:3, v/v). LPZ solution for intraduodenal administration was prepared after LPZ powder was dissolved with either surfactant, Tween 80, Labrasol or HCO-60, and thereafter K_2CO_3 was added as a stabilizer of LPZ as shown in Table 1. LPZ, 500 mg, was initially dissolved in 2.0 mL of acetone, and then either surfactant, 60 or 170 mg of HCO-60, 170 mg of Tween 80 or 10 or 170 mg of Labrasol, was added. Finally, 5 mg of potassium carbonate and adsorbent were added. After mixed well, the solvent was removed under reduced pressure. Enteric LPZ capsule was prepared by filling the solid preparation in a size 000 enteric capsule made of hydroxypropylmethyl cellulose phthalate.

2.3. Dissolution experiment

Solid preparations were used for in vitro dissolution experiment using 100 mL of pH 9.3 bicarbonate buffer according to the method used for omeprazole, under the rotation speed of 150 rpm at 37 °C (Choi et al., 2000). At the predetermined time, 0.3 mL of sample was collected from the dissolution medium and thereafter the same amount of fresh medium was replaced. The collected samples were filtered through a Millex-LG filter (0.2 μm, Milipore Corp., MA, USA) and was used for the assay of LPZ by HPLC. The time, T50%, when the half amount of total LPZ was released from the test preparation was used to show the release rate of LPZ from the system.

2.4. Animal experiment

2.4.1. Absorption experiment in rats

Male Wistar strain rats (310–350 g) fasted overnight for at least 12 h were used in the study. The rats were anaesthetized by an intraperitoneal administration of sodium pentobarbital solution, 50 mg/kg. Before the abdominal incision, control blood sample, 0.45 mL, was obtained from the carotid vein by making a small incision. Next, the abdominal incision was performed and upper small intestine was isolated. A small incision was made in the duodenum and the test LPZ solid preparation was inserted at a dose of 5.0 mg/kg. After the abdominal incision was sutured, blood samples, 0.45 mL, were collected from the right jugular vein at 0.5, 1, 1.5, 2, 3, 4 and 5 h after administration. Plasma fraction was obtained from whole blood by centrifugation at 12,000 rpm for 10 min at 4 °C using KUBOTA 1720 (Tokyo, Japan), and then stored at −80 °C until analysis.

2.4.2. Intravenous administration experiment in rats

Male Wistar stain rats (290–355 g) fasted overnight for at least 12 h were used in the study. The rats were anesthetized by an intraperitoneal administration of sodium pentobarbital solution, 50 mg/kg. LPZ solution was intravenously injected, 2.0 mg/kg, to the left carotid vein and blood samples, 0.45 mL, were obtained from the right carotid vein at 2, 5, 10, 20, 30 min,

1, 2, 3 and 4 h. Plasma fraction was obtained and stored as noted above.

2.4.3. Absorption experiment in dogs

Three adult male beagle dogs (weighing 10.0–12.1 kg) were fasted overnight for at least 12 h, although free access to water was allowed. However, during the course of the experiment, water was not given until 4 h after the test preparation was administered. The dogs received the test LPZ preparation once a week and cross-over study was performed with a washing out period of 1 week. Each dog received an oral administration of one test capsule in all studies. At 4 h after administration, a solid meal of commercial food, 450 g, and water were given. No additional food was given during the study. All experiments were carried out at the same time of the day to exclude the influences by circadian rhythm. Drug administration was carried out at 10:30 a.m. with 50 mL of water. At 30 min before drug administration, a control blood sample (1.0 mL) was obtained from the jugular vein. Each dog received one capsule, which contained 50 mg of LPZ. After oral administration of the test preparation, 1.0 mL blood samples were collected from the jugular vein at 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 h. The plasma fraction used for LPZ assay was obtained by centrifuging the blood samples at 12,000 rpm for 10 min. These plasma samples were immediately frozen at −80 °C until analysis.

All experiments using rats and beagle dogs were approved by the animal care and use committee of Kyoto Pharmaceutical University and were performed in accordance with the standards listed in the "Guideline for Animal Experimentation (1987)" published by the Japanese Association for Laboratory Animal Science.

2.4.4. Intravenous administration experiment in dogs

After a week of oral administration study, an i.v. solution of LPZ was injected to the same dogs, 2.0 mg/kg. After injection, blood samples, 1.0 mL, were also collected at 2, 15, 30 min, 1, 1.5, 2, 3, 4 and 6 h. Plasma fraction was obtained and stored as noted above.

2.5. Plasma LPZ assay

The plasma LPZ concentrations were determined by a HPLC analysis method according to Aoki et al. (Aoki et al., 1991). LPZ was extracted from the plasma sample by liquid–liquid extraction method. At first, 200 μL of a plasma sample was extracted with 5 mL of diethylether-dichlorlmethane (7:3, v/v). After centrifugation (3000 rpm, 10 min) using KUBOTA 1720 (Tokyo, Japan), the supernatant was evaporated to dryness under the flow of N_2 gas and was reconstituted with 200 μL of the mobile phase of which 100 μL was injected to HPLC system. The HPLC system consisted of a Shimadzu LC-10AS as a pump, Shimadzu LC-10AV as a detector equipped with an autosampler AS-8020 (Tosoh, Tokyo, Japan). The analytical column was a LiChrosorb Rp-18, (particle size 5 μm; 250 mm × 4.6 mm i.d., Kanto Chemical, Tokyo, Japan). The mobile phase was the mixture of acetonitrile-water-*n*-octyl amine (650: 350: 1), adjusted to pH7.0 with phosphoric acid. The column temperature and the flow rate was 40 °C and 1.0 mL/min, respectively. LPZ was detected at 285 nm. A set of seven calibration standards was run with each series of the samples. The inter-day variations were less than 7.0%. Linear calibrations were obtained between 0 and 10 μg/mL and the correlation coefficients were greater than 0.99. The limit of quantification was 10 ng/mL.

2.6. Pharmacokinetic analysis

The following pharmacokinetic parameters were determined from the plasma LPZ concentration-time data by a noncompartmental pharmacokinetic analysis method using WinHARMONY software developed by us (Yoshikawa et al., 1998). The time when plasma drug concentration reaches its maximum concentration (T_{max}), and the peak plasma drug concentration (C_{max}), were determined from the authentic plasma concentration-time data. The elimination rate constant (λ_z), was determined from the slope of the terminal phase of the concentration versus time profile. The area under the plasma drug concentration versus time curve (AUC) and the area under the first-moment curve (AUMC) after oral administration of the test preparations were calculated using the linear trapezoidal rule up to the last measured plasma LPZ concentration. The mean residence time (MRT) after oral administration was calculated by AUMC/AUC.

2.7. Statistical analysis

All values were expressed as their mean ± S.E.. Means of two groups were compared using non-paired Student's *t*-test. A value of $p < 0.05$ or $p < 0.01$ was considered statistically significant.

3. Results

As LPZ is insoluble in water, three surfactants, Tween 80, HCO-60 and Labrasol, were used to accelerate the solubility of LPZ and the prepared solution was administered into the duodenum of rats, 5.0 mg/kg. Fig. 1 shows the plasma LPZ concentration versus time profiles after administration of the four solutions and the powder preparation (powder A) as a reference. The plasma LPZ levels were dependent on the used surfactant to dissolve LPZ. Among them, HCO-60 (solution D) showed the highest C_{max}, 0.46 ± 0.01 μg/mL. On the contrary, Tween 80 (solution B) showed the lowest C_{max}. The pharmacokinetic parameter values were calculated and are shown in Table 2. The AUC of the three liquid preparations were 0.25 ± 0.01 μg h/mL (solution B), 0.53 ± 0.15 μg h/mL (solution C) and 0.73 ± 0.03 μg h/mL (solution D), respectively. To study the effect of formulated amount of surfactant, the solution E and solution F were prepared, with less amount of HCO-60, 60 mg, and were studied with the same method. Although the AUC of solution E, 0.58 ± 0.21 μg h/mL, was not higher than solution D, the significant difference was detected from powder A. Therefore, the absorption enhancing effect was also found out even in the case of less formulated HCO-60. However, in the case of solution F, the synergistic effect of the less HCO-60 and the Labrasol was not obtained in the absorption enhancement of LPZ. To determine the absolute BA of LPZ from the oral liquid preparations, LPZ was i.v. injected to another group of rats, where the dose was 2.0 mg/kg as shown in Fig. 2. The plasma LPZ concentration versus time profile showed a two-exponential decay and the pharmacokinetic parameters were determined by a non-compartment analysis method and the results are also shown in Table 3. The AUC was 0.75 ± 0.12 μg h/mL. By comparing the AUCs obtained after intraduodenal administration and i.v. injection, the absolute BA of LPZ was 5.5% (powder A), 13.6% (solution B), 28.1% (solution C), 39.0% (solution D), 30.9% (solution E) and 23.8% (solution F), respectively. As HCO-60 showed the highest BA of LPZ among the used surfactants, liquid preparation containing HCO-60 as a solubilizer was used for the second step study where solid preparations composed

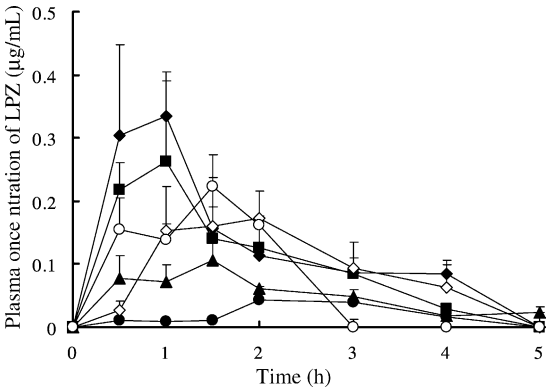

Fig. 1. Plasma LPZ concentration-time profiles after intraduodenal administration of LPZ test preparations to rats, 5 mg/kg, (●): powder A; (▲): solution B; (■): solution C; (♦): solution D; (◇): solution E and (○): solution F. Each point shows the mean ± S.E. of four rats.

Table 2
Pharmacokinetic parameters of LPZ after intraduodenal administration of LPZ test preparations to rats

Preparation code name	C_{max} (μg/mL)	T_{max} (h)	$t_{1/2}$ (h)	MRT (h)	$AUC_{0-\infty}$ (μg h/mL)	BA (%)
A	0.04 ± 0.02	1.67 ± 0.88	0.11 ± 0.05	1.69 ± 0.88	0.10 ± 0.05	5.53
B	0.14 ± 0.02	1.00 ± 0.29	0.71 ± 0.42	2.13 ± 0.34	0.25 ± 0.01	13.6
C	0.33 ± 0.09**	0.75 ± 0.14	0.43 ± 0.15	1.72 ± 0.14	0.53 ± 0.15*	28.1
D	0.46 ± 0.01**	0.67 ± 0.17	1.10 ± 0.43*	2.32 ± 0.49	0.73 ± 0.03**	39.0
E	0.21 ± 0.04	2.17 ± 0.44	0.68 ± 0.53	2.59 ± 0.33	0.58 ± 0.21*	30.9
F	0.26 ± 0.03**	1.17 ± 0.33	0.47 ± 0.35	1.76 ± 0.43	0.45 ± 0.05	23.8

Each value represents the mean ± S.E. of four rats.
*$p < 0.05$ significantly different from LPZ powder (preparation A).
**$p < 0.01$ significantly different from LPZ powder (preparation A).

Table 3
Pharmacokinetic parameters of LPZ after intravenous administration of LPZ solution, 2 mg/kg

	C_{max} (μg/mL)	λ_z (h^{-1})	$t_{1/2}$ (h)	MRT (h)	$AUC_{0-\infty}$ (μg h/mL)
Rat	1.41 ± 0.02	0.75 ± 0.01	0.92 ± 0.23	1.13 ± 0.11	0.75 ± 0.12
Dog	1.19 ± 0.13	0.70 ± 0.05	1.00 ± 0.14	1.12 ± 0.16	1.20 ± 0.23

Each value represents the mean ± S.E. of four rats.

of microparticles holding LPZ solution was used. As adsorbents, Sylysia, Neusilin and Florite were used. Five preparations shown in Table 1 were prepared and the dissolution study on LPZ from the preparations was performed. Fig. 3 shows the results of the in vitro dissolution experiment. The release rate of LPZ from Neusilin NS_2N (preparation J), US_2 (preparation K) and Florite RE (preparation L) systems were slow, i.e., T50% of LPZ was longer than 1.0 h. As the small intestinal transit time of solid preparation in rats is approximately 2 h, two preparations having slow release rate, Neusilin US_2 and Florite RE were not used in the following in vivo absorption experiment in rats. Also, Neusilin NS_2N system had the T50% of 0.4 h, in vivo evaluation was not performed. Then, three solid preparations, Sylysia 550 (preparation G), 320 (preparation H) and Neusilin S_2 (preparation I) were evaluated in vivo absorption study and the result is shown in Fig. 4. The pharmacokinetic parameters were shown in Table 4. After administration, Sylysia 550 system showed C_{max} of LPZ, 0.41 ± 0.09 μg/mL

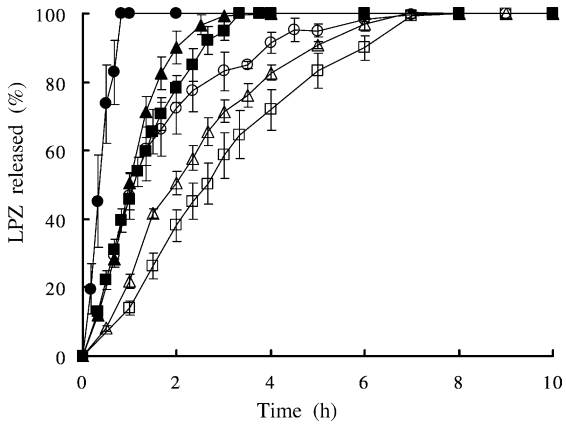

Fig. 3. Dissolution profiles of LPZ from different LPZ solid preparations, (●): preparation G; (▲): preparation H; (■): preparation I; (○): preparation J; (△): preparation K and (□): preparation L. Each point shows the mean ± S.E. of four experiments.

at 0.5 h. However, the other two systems had T_{max} of about 1.0 h. T_{max} was correlated well with the T50% of LPZ in the in vitro dissolution experiment. C_{max} of Sylysia 550 system was higher than that of the other

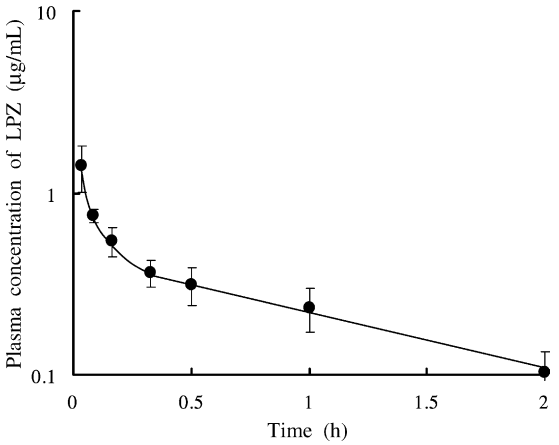

Fig. 2. Plasma LPZ concentration-time profiles after intravenous administration of LPZ solution, 2 mg/kg. Each point shows the mean ± S.E. of four rats.

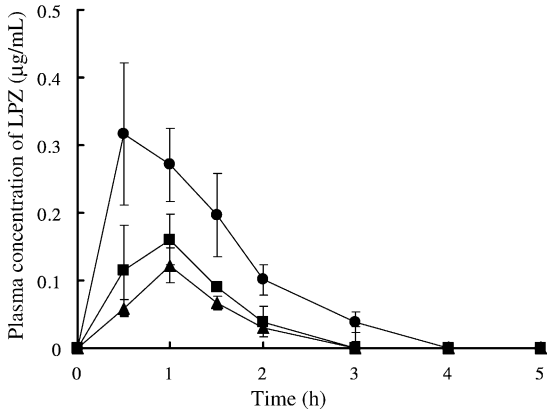

Fig. 4. Plasma LPZ concentration-time profiles after intraduodenal administration of LPZ solid preparations to rats, 5 mg/kg, (●): preparation G, (▲): preparation H, (■): preparation I. Each point shows the mean ± S.E. of four rats.

Table 4
Pharmacokinetic parameters of LPZ after intraduodenal administration of LPZ test preparations to rats

Preparation	C_{max} (μg/mL)	T_{max} (h)	$t_{1/2}$ (h)	MRT (h)	$AUC_{0-\infty}$ (μg h/mL)	BA (%)
G	$0.41 \pm 0.09^{**}$	0.75 ± 0.11	0.57 ± 0.20	1.44 ± 0.16	$0.53 \pm 0.08^{**}$	28.1
H	0.12 ± 0.03	1.00 ± 0.00	0.09 ± 0.00	1.39 ± 0.13	0.17 ± 0.02	8.86
I	0.18 ± 0.04	0.83 ± 0.17	$0.77 \pm 0.31^{*}$	2.05 ± 0.11	0.29 ± 0.09	15.7

Each value represents the mean ± S.E. of four rats.
* $p < 0.05$ significantly different from LPZ powder (preparation A).
** $p < 0.01$ significantly different from LPZ powder (preparation A).

two systems. By comparing the AUC, the absolute BA of LPZ from Sylysia 550 system was determined to be 28.1%.

As the Sylysia 550 system showed the highest BA in the rat study, the system was further evaluated in dogs. The Sylysia 550 system containing LPZ dissolved with HCO-60 solution was filled in an enteric capsule made of HP-55 of which threshold dissolution pH was 5.5, because LPZ is unstable against the hydrochloric acid in the stomach. HP-55 is a commonly used enteric polymer for the coating of tablet. We have been studying a colon delivery capsule for one decade and prepared many colon delivery capsules containing intestinal pressure-controlled colon delivery capsule (Jeong et al., 2001). According to the same preparation method, enteric capsule was prepared and was used in this experiment. Using three beagle dogs, Sylysia 550 system was orally administered and the plasma LPZ levels versus time profile were evaluated. Table 5 shows the pharmacokinetic parameters after oral administration of Sylysia 550 system and an enteric LPZ tablet as a reference preparation. The AUC of these preparations were 2.16 ± 0.26 μg h/mL (Sylysia 550), 0.80 ± 0.10 μg h/mL (tablet), respectively. In the case of i.v. administration, plasma LPZ level decreased semi-logarithmically as shown in Fig. 5. Pharmacokinetic parameters were calculated and are shown in Table 3. The AUC was 1.20 ± 0.23 μg h/mL. By comparing the AUCs of the two profiles, the absolute BA of LPZ from Sylysia 550 system was 71.7%.

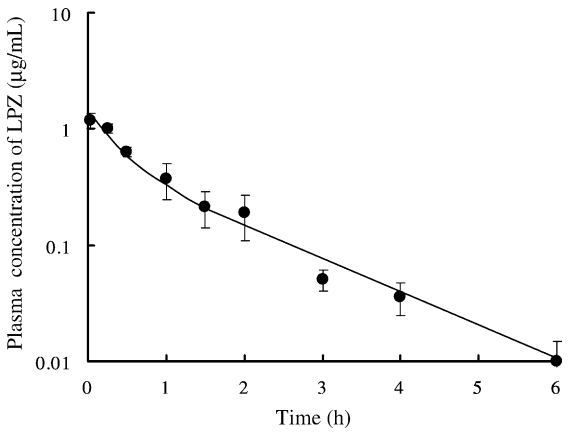

Fig. 5. Plasma LPZ concentration-time profiles after intravenous administration of LPZ solution to dogs, 2 mg/kg. Each point shows the mean ± S.E. of three dogs.

4. Discussion

LPZ has been clinically used in the therapy of gastric and duodenal ulcerative disease for a long time (Tateno and Nakamura, 1991). Although LPZ shows a wide inter-subject variation on its BA as omeprazole, LPZ does not belong to the drug category that must

Table 5
Pharmacokinetic parameters of LPZ after oral administration of LPZ test preparations to dogs

Preparation	C_{max} (μg/mL)	T_{max} (h)	$t_{1/2}$ (h)	MRT (h)	$AUC_{0-\infty}$ (μg h/mL)	BA (%)
G	$1.21 \pm 0.15^{**}$	2.75 ± 0.25	0.66 ± 0.18	$3.44 \pm 0.19^{*}$	$2.16 \pm 0.26^{**}$	71.7
Reference	0.41 ± 0.03	1.50 ± 0.50	0.93 ± 0.13	2.08 ± 0.33	0.80 ± 0.10	26.5

Each value represents the mean ± S.E. of four dogs.
* $p < 0.05$ significantly different from reference preparation.
** $p < 0.01$ significantly different from reference preparation.

be carefully used under the TDM practice because of its high therapeutic index. Omeprazole has a BA between 35 and 63% (Andersson et al., 1990; Hatlebakk and Berstad, 1996). We wanted to ascertain whether LPZ has a low BA as omeprazole. Poor BA is usually ascribed to: (1) the inactivation of the drug by the gastric acid or (2) poor membrane permeability or (3) to the pre-systemic or systemic first-pass metabolism. Furthermore, plasma omeprazole levels exhibit a high inter-subject variation, which was also expected to be the case for LPZ. When we evaluated LPZ preparation in human volunteers, the genotype would affect the BA of LPZ, because the hepatic metabolic clearance of LPZ is dependent on the CYP2C19 genotype as in the case of omeprazole (Iwasaki et al., 2004). However, in the case of experimental animals like rats and dogs, inter-subject variation of the LPZ metabolic clearance rate does not contribute to the wide inter-subject variation on its BA. Many factors affect the BA of LPZ. They are: (1) degradation in the acid, (2) dissolution rate in the small intestine, (3) membrane permeability and (4) metabolism in the liver. LPZ belongs to the class II compound with low solubility and high membrane permeability according to the classification by Amidon et al. (Amidon et al., 1995 and Yu et al., 2002). Therefore, the solubility problem is the priority number one project to solve. Clinically supplied preparation is enteric-coated granules filled in a gelatin capsule, because of its low stability in the acidic condition, i.e., stomach. As compared to the stomach, there is less water in the small intestine. Therefore, the dissolution rate of LPZ from the enteric preparation has an important role on the BA of LPZ. To increase the dissolution rate of LPZ, three non-ionic surfactants were used in this study. The HLB of them are 15 for Tween 80, 14 for both HCO-60 and Labrasol. By judging from these HLB values, Tween 80 might show the highest effect on the dissolution and absorption of LPZ. However, HCO-60 showed the highest BA. Generally speaking, it is concerned that most surfactants have some effects on the small intestinal mucosa. It is better to decrease the formulated amount of surfactant in the test preparation. Therefore, the amount of HCO-60 was decreased in the preparation E. The BA of LPZ from preparation E was less than that of the preparation D, but it had a significant difference against powder preparation A. To solidify the LPZ HCO-60 solution, several adsorbents were used. Sylysia is light anhydrous silicic acid and was qualified as a pharmaceutical additive. It is used to pulverize liquid formulation and is also used in tablet. Neusilin, magnesium aluminometasilicate , has an antacid effect. Florite, calcium silicate, is used for the solidification of oily preparation. The formulated amount of such adsorbent differs in each preparation because of their capacity to adsorb liquid preparation. The specific surface areas of their adsorbents are 500 m^2/g for Sylysia 550, 300 m^2/g for Sylysia 320 and 110 m^2/g for Neusilin S_2, respectively. Microporous silicate, especially Sylysia 550, has the biggest specific surface area. On the other hand, the mean diameter of Sylysia 550, 320 and Neusillin S_2 are 3.9, 3.2 and 100 μm, respectively. As the diameter decreases, the particles are well dispersed and thought to penetrate into the microville of the small intestine. Therefore, Sylysia 550 system showed the highest BA of LPZ.

When we evaluated Sylysia 550 system filled in an enteric capsule in dogs, an absorption lag-time, approximately 1 h, was observed. As the Sylysia system is a single unit system, such an absorption lag-time was obtained. Coupe et al. (1991) showed that single unit dosage forms had left the small intestine already 180 min after oral administration, while 50% of a particulate multi-unit delivery system was still present in the small intestine after 200 min. Moreover, Tateno and Nakamura (1991) reported that multiple unit system had a shorter absorption lag-time than single unit system. Therefore, multiple unit system can offer the advantages of the prolonged gastrointestinal-resistance and the shorter absorption lag-time. This system was introduced to LPZ preparation, Takepron™. In the next study, we want to evaluate our LPZ system in comparison to this multiple unit system.

In conclusion, new oral solid dosage form of LPZ has been prepared using surfactant and adsorbent. The BA of LPZ was dependent on both surfactant and adsorbent. The combination of HCO-60 and Sylysia 550 showed the highest BA in rats, i.e., 28.1%. The system was filled in an enteric capsule made of HP-55 and was evaluated in dogs by an oral administration. The BA of LPZ from enteric capsule was 71.7%. In our laboratory, when this system was used for gentamicin, the good results, which are submitted now, were obtained. Therefore, this system will be contributory to the improvement of the intestinal absorption for omeprazole

having a wide inter-subject variation or similar molecular weight drug with lansoprazole.

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