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In vitro and *in vivo* sustained-release characteristics of theophylline matrix tablets and novel cluster tablets

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Abstract

We compared the *in vitro*/*in vivo* properties of theophylline between two sustained-release preparations, which are administered once a day. Tablet A is a swelling/disintegration-type matrix tablet consisting of hydrophobic wax granules and hydrophilic polymer granules (cluster tablets). Tablet B is a matrix tablet consisting of hydrophilic polymer granules.

We conducted a dissolution test with JPXIV *in vitro*, and compared the results between the two preparations. Neither pH nor agitation intensity influenced these preparations. After they were immersed in oleic acid, there were no marked changes in the dissolution properties in the dissolution test.

After administration of Tablets A and B containing theophylline at 200 mg to fasted dogs, we compared plasma level profiles of theophylline. The mean plasma level of theophylline gradually increased to a maximum (7.17 μg/mL) 4 h after administration of Tablet A. After administration of Tablet B, a similar finding was noted, with a maximum of 6.09 μg/mL. Tablet B showed a higher coefficient of variation (CV) for the plasma level at each point.

Subsequently, we administered two tablets of preparations A and B containing theophylline at 200 mg to healthy volunteers who had not been fasted, and compared plasma level concentration of theophylline. The mean plasma level of theophylline gradually increased to a maximum (6.09 μg/mL) 12 h after administration of Tablet A, but then decreased, with a half-life of 9.10 h. After administration of Tablet B, a similar finding was noted, with a maximum of 7.87 μg/mL and a half-life of 7.76 h. Tablet A showed a significantly higher plasma concentration 1 and 2 h after administration; however, there were no significant differences at other points. The C_{max} of Tablet B was significantly higher than that of Tablet A. However, there were no significant differences in other pharmacokinetic parameters between the two preparations.

The T_{max} of Tablet A was 10–12 h after administration, relatively constant. However, that of Tablet B was 10–18 h after administration. The CV for T_{max} was 9.8% for Tablet A and 22.0% for Tablet B. After administration of Tablet B, the plasma level of theophylline varied at each point. Based on these results, inter-subject variations after administration of Tablet A may be less marked than those after administration of Tablet B. It is concluded that, the cluster tablets A developed in this study showed significantly less inter-subject variation of theophylline plasma levels than the conventional matrix tablets B.

Keywords: Theophylline; Cluster tablets; Matrix tablets; Sustained release; Hydrophobic wax; Hydrophilic polymer

1. Introduction

Tablets are more commonly prescribed compared to capsules and granules due to its simple dosage form. Recently, techniques for manufacturing sustained-release preparations have advanced to reduce patient stress and improve quality of life (QOL) by decreasing the frequency of administration.

Oral sustained-release preparations are classified into two types: multiple unit preparations and single unit preparations. After administration of multiple unit preparations, granules are relatively extensively distributed in the digestive tract. Therefore, digestive tract movement does not influence these preparations, and there was no differences among the results of

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pharmacokinetic studies (Efentakis and Koutlis, 2001; Sandberg et al., 1993).

In manufacturing multiple unit preparations, spherical granules are routinely coated with sustained-release material, and a large volume of organic solvent is employed. There are some types of water-based coating solution for sustained-release processing (Frohoff-Hülsmann et al., 1999), however, mixed solvents such as ethanol is used in most preparations. Concerning granule coating with a fluid bed coating machine, even when the same prescription is employed, the release properties of the main drug differ between a preparation manufactured using an experimental small-scale machine and that manufactured using a large-scale manufacturing machine due to scale-up-related differences in drying/agitation efficiency between an experimental machine and a manufacturing machine, influencing the reproducibility of dissolution (Aoki et al., 1998; Ohkuma et al., 1998).

Single-unit preparations include coating tablets coated with release-controlling film, tablets with water-soluble polymer matrix (Madhusudan Rao et al., 2001; Rao et al., 2001), tablets with wax matrix (Zhang and Schwartz, 2003), and tablets with hydrophobic polymer matrix (Katikaneni et al., 1995; Neau et al., 1999). The release of the main drug is readily influenced by diet and peristalsis of the digestive tract in comparison to multiple unit preparations, leading to differences in the results of pharmacokinetic studies.

Theophylline, which we employed in this study, has previously been administered to treat bronchial asthma. However, the range of therapeutic concentrations is restricted (Mitenko and Ogilvie, 1973; Koup et al., 1976), and absorption is readily influenced by diet (Karim, 1986), medication management is difficult.

In conventional sustained-release preparations, it is difficult to regulate the rate of drug release, and the rate of drug release varies among lots due to a complex manufacturing process. Thus, advanced techniques are required to maintain stable quality.

In this study, we investigated cluster tablets; we manufactured sustained-release granules consisting of a hydrophobic wax matrix base and sustained-release granules consisting of a hydrophilic polymer matrix base by the standard granulating method, differing from the granule coating method with organic solvent. We conducted dissolution and pharmacokinetic tests in dogs and human volunteers to compare the cluster tablets with conventional gel matrix tablets.

2. Experimental methods

2.1. Materials

We used theophylline (Shiratori Pharmaceutical Co., Ltd.), lactose (200 M, Megre), hydroxypropylmethylcellulose (HPMC) 2208 (Metorose® 90SH viscosity 4000 mm^2/s, viscosity 100,000, Shin-Etsu Chemical Co., Ltd.), microcrystalline cellulose (Avicel® PH101, Asahi Kasei Corporation), stearic acid (NAA-174, NOF Corporation), hydrogenated oil (Lubriwax® 101, FREUND), and magnesium stearate (Taihei Chemical Industrial Co., Ltd.) in accordance with the Japanese Pharmacopoeia (JPXIV). We used ethylcellulose aqueous dispersion (Aquacoat®, Asahi Kasei Corporation) and hydroxypropylmethylcellulose acetate succinate (HPMCAS) (AQOAT®, Shin-Etsu Chemical Co., Ltd.) in accordance with the Japanese Pharmaceutical Excipients. We used glycerol esters of fatty acids (Excel 84®, Kao Corporation, Myvacet® 9-45K, Koyo Mercantile Company Ltd.) in accordance with the Japan's Specifications and Standards for Food Additives. Other reagents were commercially available special-grade products.

2.2. Preparation of sustained-release tablets

2.2.1. Tablet A

Tablets with a combination of hydrophilic polymer granule-1 and hydrophobic wax granules.

2.2.1.1. Preparation of hydrophilic polymer granule-1. The mixture of theophylline (600 g), hydroxypropylmethylcellulose 2208 (50 g), and lactose (350 g) was kneaded with purified water, dried, and sized with 16-mesh (1000 μm) sieve to prepare hydrophilic polymer granules.

2.2.1.2. Hydrophobic wax granules. Stearic acid (140 g), hydrogenated oil (130 g), and glycerol esters of fatty acids (130 g) were heated, dissolved, and added to theophylline (600 g). After kneading and cooling, this was sized with 16-mesh (1000 μm) sieve to prepare hydrophobic wax granules.

As samples for dissolution and pharmacokinetic tests, the above hydrophilic polymer granules at 166.8 mg were mixed with hydrophobic wax granules at 166.8 mg and magnesium stearate at 3.4 mg to prepare 337.0 mg oblong tablets (13 mm in long diameter and 8 mm in short diameter). In consideration of easy ingestion by patients, oblong tablets were prepared.

2.2.2. Tablet B

Tablets with a combination of hydrophobic ethylcellulose granules and hydrophilic polymer granules-2.

2.2.2.1. Preparation of hydrophobic ethylcellulose granules. Theophylline (600 g) was mixed with microcrystalline cellulose (50 g), lactose (30 g), hydrogenated oil (150 g), and hydroxypropylmethylcellulose 2208 (Metorose® viscosity 100,000 mm^2/s, 50 g). Then, the mixture of ethylcellulose aqueous dispersion (333.3 g) and glycerol esters of fatty acids (Myvacet®, 9-45K, 20 g) was added, kneaded, granulated dried, and sized with 16-mesh (1000 μm) sieve to prepare hydrophobic ethylcellulose granules.

2.2.2.2. Preparation of hydrophilic polymer granules-2. Theophylline (600 g) was mixed with microcrystalline cellulose (100 g), lactose (100 g), hydroxypropylmethylcellulose 2208 (Metorose®, viscosity 100,000 mm^2/s, 150 g), and hydroxypropylmethylcellulose acetate succinate (50 g). The mixture was kneaded with 25% aqueous solution of ethanol (JP), dried, and sized with 16-mesh (1000 μm) sieve to prepare hydrophilic polymer granules-2.

As samples for dissolution and pharmacokinetic tests, the above hydrophobic ethylcellulose granules at 166.8 mg were mixed with hydrophilic polymer granules-2 at 166.8 mg and magnesium stearate at 3.4 mg to prepare 337.0 mg oblong tablets (13 mm in long diameter and 8 mm in short diameter).

2.3. Dissolution test

An *in vitro* dissolution test using tablets was conducted according to the paddle method (900 mL) described in the JPXIV.

2.3.1. Influence of pH

Purified water, pH 1.2 (first fluid of disintegration test method, JPXIV), pH 4.0 (acetic acid/sodium acetate buffer), pH 6.8 (second fluid of disintegration test method, JPXIV), pH 7.5 (simulated intestinal fluid, monobasic potassium phosphate/sodium hydroxide buffer), paddle rotation speed: 50 rpm.

2.3.2. Under a severe condition

We used the purified water and we added 500 nylon beads (Ø5.5 mm). Paddle rotation speed was 100 rpm.

2.3.3. Influence of wet conditions

We used the second fluid (pH 6.8) in the disintegration test method described in the JPXIV. As a surfactant, we added polysorbate 80 at concentrations of 0%, 0.1%, 0.5%, and 1.0%. The paddle rotation speed was 50 rpm.

2.3.4. Prediction of the influence of diet in an in vitro study

Samples were immersed in 50 mL of oleic acid (37 °C) for 1 or 3 h, and a dissolution test was conducted using the second fluid (in the disintegration test method described in the JPXIV) containing 0.1% polysorbate 80. The paddle rotation speed was 50 rpm.

To investigate the influence of pH and agitation intensity, theophylline dissolution was measured by the UV method. To examine the influence of wet conditions/diet, it was measured by high performance liquid chromatography (HPLC).

2.4. Measurement of plasma drug levels

2.4.1. Plasma level of theophylline in dogs

Plasma samples at 100 μL were placed in a 10 mL glass centrifuge tube, and mixed with 100 μL of acetonitrile, 100 μL of internal standard substance solution (β-hydroxyethyltheophylline/acetonitrile solution, 20 μg/mL), and 3 mL of acetonitrile. The solution was reacted for 5 min, and centrifuged at 2500 rpm for 10 min to isolate 2.5 mL of the supernatant in a 10-mL glass centrifuge tube. The supernatant was dried under reduced pressure (30 °C), dissolved in 0.2 mL of the mobile phase, and filtrated with a 0.45-μm membrane filter. The solution at 50 μL was quantified by HPLC under the following conditions: precolumn, TCI OPTI-GUARD Fit ODS 1 mm i.d. × 15 mm (Tokyo Kasei Kogyo Co., Ltd.); main column, L-column ODS 4.6 mm i.d. × 250 mm (Chemicals Evaluation and Research Institute, Japan); flow rate, 1.0 mL/min; detector, UV 280 nm; column temperature, 45 °C; and mobile phase, solution consisting of 0.01 mol/L sodium acetate solution (pH 4.75) and methanol at a ratio of 88:12 (v/v).

2.4.2. Plasma level of theophylline in humans

We modified the method described by Rogge et al. (1988). Plasma at 0.2 mL was mixed with 50 μL of purified water and 20 μL of internal standard substance solution (β-hydroxytheophylline solution, 50 μg/mL) and 3.0 mL of acetonitrile. After shaking for 10 min, it was centrifuged at 2500 rpm for 10 min, and 2.5 mL of the supernatant was dried under reduced pressure (30 °C). The residue was mixed with 200 μL of mobile phase solution A. The solution at 40 μL was quantified by HPLC (gradient method) under the following conditions: precolumn, Nucleosil® 100-5C18 (Ø4.6 mm × 50 mm GL Sciences Inc.); main column, Nucleosil® 100-5C18 (Ø4.6 mm × 250 mm); flow rate, 1.0 mL/min; detector, UV 280 nm; column temperature, 50 °C; and mobile phase, solution A (solution containing 0.01 M sodium acetate and 0.005 M tetrabutylammonium sulfate hydride was mixed with 10N sodium hydroxide solution to prepare a pH value of 4.75) and solution B containing solution A and methanol at a ratio of 1:1.

Gradient conditions:

1. Before the start of measurement, the percent volume of solution A was 91%, and that of solution B was 9%. These solutions were added so that the percent volume was 78% and 22%, respectively, 10 min after the start of measurement.
2. Solutions A and B were added so that the percent volume was 70% and 30%, respectively, 10–25 min after the start of measurement.
3. Solutions A and B were added so that the percent volume was 60% and 40%, respectively, 25–30 min after the start of measurement.
4. Solutions A and B were added so that the percent volume was 54% and 46%, respectively, 30–31 min after the start of measurement.
5. Solutions A and B were added so that the percent volume was 91% and 9%, respectively, 31–31.1 min after the start of measurement, and this was continued until 50 min after the start of measurement.
6. Subsequent measurement was performed.

The above gradient conditions of HPLC are summarized in Table 1.

Table 1
Gradient conditions of HPLC

Time (min)	Solution A (%)	Solution B (%)
0	91	9
10	78	22
25	70	30
30	60	40
31	54	46
31.1	91	9
50	91	9

2.5. Pharmacokinetic study in dogs

A pharmacokinetic study of the test tablets was performed.

We randomly divided six Beagles into two groups. After these dogs were fasted, Tablets A and B were administered by the crossover method. A sustained-release oblong tablet containing 200 mg of theophylline was orally administered with 50 mL of water. Blood was collected before administration and 1, 2, 4, 8, 12, 24, 28, 32, and 48 h after administration. The plasma level of theophylline was measured by HPLC.

2.6. Pharmacokinetic study in humans

A pharmacokinetic study of the test tablets was performed.

The subjects were 10 healthy male volunteers. They were randomly divided into two groups. Tablets A and B were administered without fasting. Standard diet was given. We orally administered two sustained-release oblong shape tablets containing 200 mg of theophylline per tablet, with 180 mL of water. Blood was collected before administration and 1, 2, 4, 6, 8, 10, 12, 15, 18, 24, 30, 36, and 48 h after administration. The plasma level of theophylline was measured by HPLC.

3. Results and discussion

3.1. Dissolution properties

A dissolution test of Tablets A and B was performed, as described below.

3.1.1. Influence of the pH value of dissolution medium

The results for Tablets A and B are shown in Fig. 1. Sustained-release preparations should not be affected by pH changes in the digestive tract (Streubel et al., 2000). Dissolution of Tablet A was slightly delayed when the pH value was 6.8. However, there was no pH-dependent dissolution. The dissolution profiles suggest that pH changes do not influence this preparation. Concerning Tablet B, there was no pH-dependent dissolution, suggesting that pH changes do not influence this preparation.

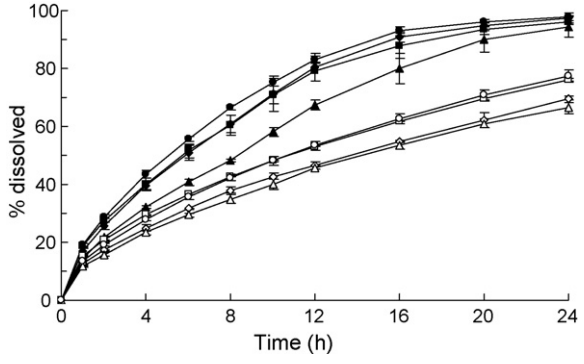

Fig. 1. Effect of the pH of dissolution medium on dissolution of theophylline from Tablet A and Tablet B using the paddle method at a rotation speed of 50 rpm. Each result shows the mean ± S.D. ($n = 3$). Tablet A: (♦) pH 1.2, (■) pH 4.0, (▲) pH 6.8, and (●) water; Tablet B: (◊) pH 1.2, (□) pH 4.0, (△) pH 6.8, and (○) water.

3.1.2. Dissolution under a severe condition

Considering the influence of various factors in the digestive tract on preparations, especially sustained-release preparations, it is important to investigate the mechanical forces of the digestive tract and diet-related physical forces. A study measured agitation intensity in a dissolution test and the degree of disintegration in a disintegration test (Kamba et al., 2003). Another study has reported the results of a dissolution test of a sustained-release preparation involving mechanical forces using beads (Aoki et al., 1993).

In our previous study (Hayashi et al., 2005), we used purified water as dissolution medium, and established the paddle rotation speed as 50, 100, and 200 rpm. The two preparations were influenced by agitation intensity at a high rotation speed; however, there was no burst of sustained-release coating granules.

In this study, we performed a dissolution test using purified water as dissolution medium in the presence or absence of 500 nylon beads (Ø5.5 mm) as a model under a severe condition. The paddle rotation speed was 100 rpm. The results for Tablets A and B are shown in Fig. 2. In comparison of Tablet A with Tablet B, Tablet A was more markedly influenced in the presence of nylon beads. This was possibly because Tablet A was swollen and disintegrated after the start of the test. Nylon bead loading less markedly influenced Tablet B compared to agitation intensity. The dissolution properties were only slightly influenced when the bead method involving mechanical forces was employed.

3.1.3. Influence of a surfactant

A study has reported the influence of dissolution medium-related wet conditions on a sustained-release preparation consisting of a hydrophilic matrix (Abrahamsson et al., 1994). We employed polysorbate 80, which is used as a surfactant in the section “Dissolution Test” in “The Guidelines for Bioequivalence Tests of Generic Drugs” in Japan.

We used the second solution (pH 6.8) in the disintegration test method described in the JPXIV, as dissolution medium, and polysorbate 80, as a surfactant, at concentrations of 0%, 0.1%, 0.5%, and 1.0%. The two preparations were not influenced by the surfactant. In particular, there was no influence on Tablet B. The results for Tablets A and B are shown in Fig. 3.

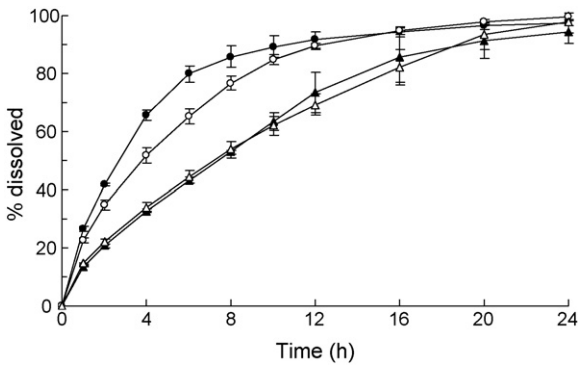

Fig. 2. Effect of the beads agitation on dissolution of theophylline from Tablet A and Tablet B using the paddle method at a rotation speed of 100 rpm in water. Each result shows the mean ± S.D. ($n = 3$). Tablet A: (●) Beads(+) and (○) Beads(−); Tablet B: (▲) Beads(+) and (△) Beads(−).

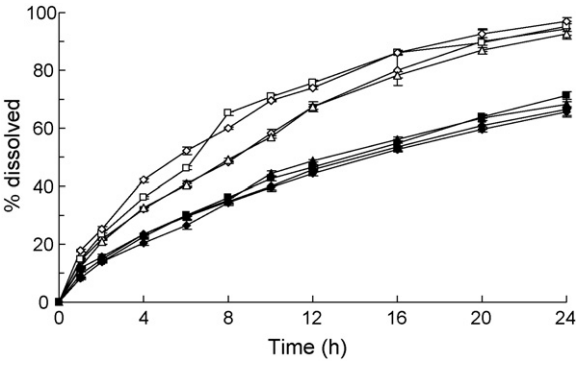

Fig. 3. Effect of the surfactant on dissolution of theophylline from Tablet A and Tablet B using the paddle method at a rotation speed of 100 rpm in JPXIV second fluid. Each result shows the mean ± S.D. ($n = 3$). Tablet A: (◊) 0%, (□) 0.1%, (△) 0.5%, and (○) 1.0%; Tablet B: (♦) 0%, (■) 0.1%, (▲) 0.5%, and (●) 1.0%.

3.1.4. Prediction of the influence of diet in an in vitro study

According to Karim, to investigate the influence of diet on a sustained-release preparation in an *in vitro* study, the preparation should be immersed in oleic acid (37 °C) for 1–3 h. Changes in the dissolution properties in the presence of a surfactant suggest that diet may influence the preparation in an *in vivo* study. Furthermore, Andonaegui et al. treated a preparation with peanut oil, and reported its influence on the preparation in a dissolution test with water (Andonaegui et al., 1999). Karim et al. employed sodium deoxycholic acid as a surfactant. However, in this study, we conducted a similar test with polysorbate 80.

After the two preparations were immersed in oleic acid (37 °C) for 1 or 3 h, a dissolution test was performed using the pH 6.8 second fluid of disintegration method JPXIV, as described above, containing 0.1% polysorbate 80, as dissolution medium. The changes in the dissolution properties of Tablets A and B were less marked than those in the absence of oleic acid, suggesting that diet does not influence these preparations. The results for Tablets A and B are shown in Fig. 4.

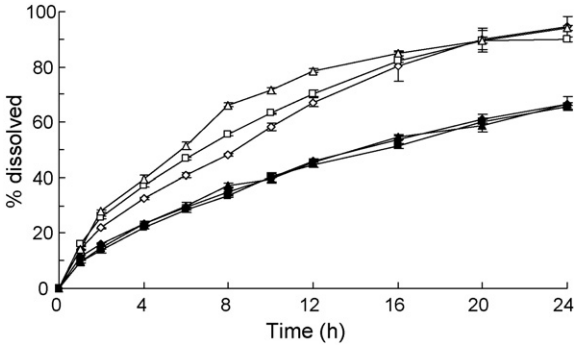

Fig. 4. Effect of the immersion time of oleic acid on dissolution of theophylline from Tablet A and Tablet B using the paddle method at a rotation speed of 50 rpm in 0.1% polysorbate 80 with JPXIV second fluid. Each result shows the mean ± S.D. ($n = 3$). Tablet A: (◊) 0 h, (□) 1 h, and (△) 3 h; Tablet B: (♦) 0 h, (■) 1 h, and (▲) 3 h.

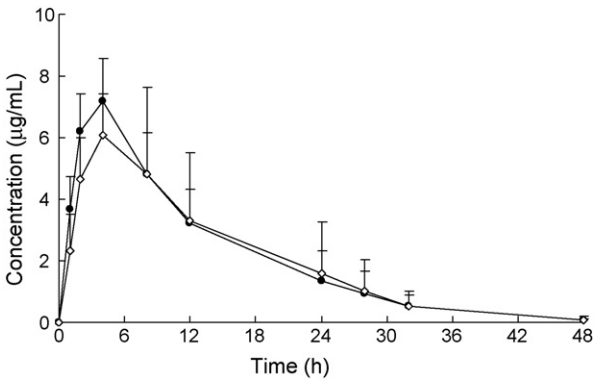

Fig. 5. Plasma theophylline concentrations as a function of time in dogs after oral administration of Tablets A and B under fasting conditions. Each result shows the mean ± S.D. ($n = 6$). (●) Tablet A and (◊) Tablet B.

3.2. Pharmacokinetic study in dogs

3.2.1. Changes in the plasma level of theophylline

We divided six Beagles into two groups, and conducted a crossover study of Tablets A and B involving fasting. The changes in the plasma drug level for 48 h after administration are shown in Fig. 5. Furthermore, the changes in the plasma drug levels after administration of Tablets A and B are shown in Figs. 6 and 7, respectively. In addition, pharmacokinetic parameters were calculated from the plasma levels, as shown in Table 2.

3.2.2. Comparison of pharmacokinetic studies

We administered the two preparations to fasted dogs, and compared changes in the plasma level of theophylline. The mean plasma level of theophylline gradually increased to a maximum (7.17 μg/mL) 4 h after administration of Tablet A, but then decreased, with a half-life of 6.28 h. The mean plasma level of theophylline gradually increased to a maximum (6.09 μg/mL) 4 h after administration of Tablet B, but then decreased, with a half-life of 6.23 h.

The values of C_{max}, a pharmacokinetic parameter, were 7.49 ± 1.12 μg/mL and 6.79 ± 2.05 μg/mL after administration of Tablets A and B, respectively. The T_{max} were 4.0 ± 2.2 h and 4.0 ± 2.2 h, respectively. The $t_{1/2}$ were

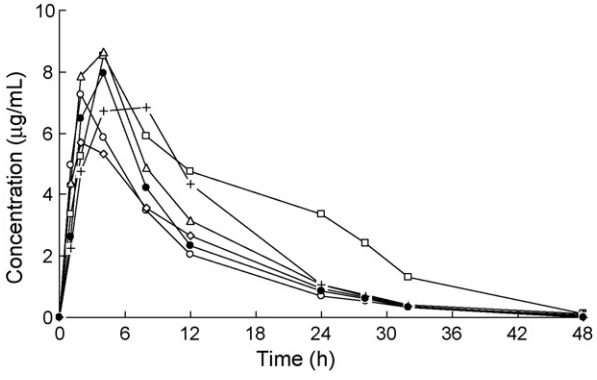

Fig. 6. Plasma theophylline concentrations as a function of time in each dog after oral administration of Tablet A under fasting conditions. (○) 1, (□) 2, (◊) 3, (△) 4, (+) 5, and (●) 6.

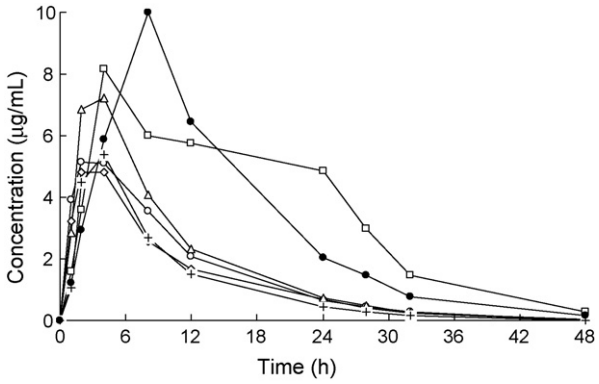

Fig. 7. Plasma theophylline concentrations as a function of time in each dog after oral administration of Tablet B under fasting conditions. (◯) 1, (□) 2, (◊) 3, (△) 4, (+) 5, and (●) 6.

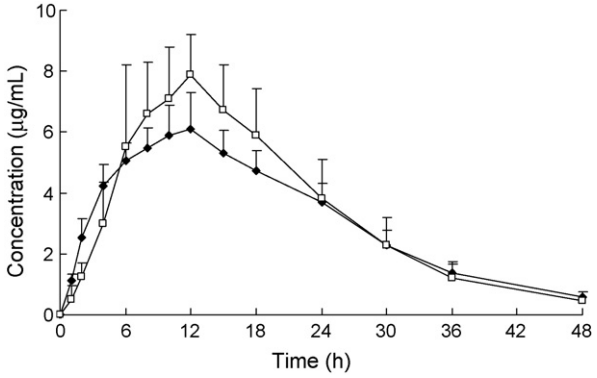

Fig. 8. Plasma theophylline concentrations as a function of time in human volunteers after oral administration of Tablets A and B under non-fasting conditions. Each result shows the mean ± S.D. ($n = 5$). (♦) Tablet A and (□) Tablet B.

6.28 ± 0.92 h and 6.23 ± 0.67 h, respectively. The $AUC_{0–48}$ were 99.57 ± 27.64 μg h/mL and 95.80 ± 49.29 μg h/mL, respectively. The $MRT_{0–48}$ were 10.89 ± 1.82 h and 11.17 ± 2.72 h, respectively. The $VRT_{0–48}$ were 77.04 ± 16.38 h and 73.26 ± 15.94 h, respectively. There were no significant differences in the pharmacokinetic parameters between the two preparations.

To investigate differences in each parameter, the coefficient of variation (CV) was compared between the two preparations. Tablet B showed higher CV for C_{max}, AUC, and MRT compared to Tablet A. In comparison of changes in the plasma level of theophylline, Tablet B showed marked differences. This may have been associated with inter-subject variations in digestive tract movement in dogs, as Tablet B is a single unit preparation. In the *in vitro* dissolution test, Tablet B showed better results. However, Tablet A showed better results in the *in vivo* test. This suggests that the influence of diffusion in the digestive tract is more marked than that of physical agitation. When the dosage form differs, that is, when the mechanism of release differs, the results of an *in vivo* test are not always correlated with those of an *in vitro* test. Considering *in vivo* diffusion, Tablet A may be more useful than Tablet B, although there were no significant differences between the two preparations.

3.3. Pharmacokinetic study in humans

3.3.1. Changes in the plasma theophylline level

We divided 10 healthy males into two groups, and administered Tablets A and B without fasting. The changes in the plasma theophylline level for 48 h after administration are shown in Fig. 8. The changes in the plasma theophylline levels after administration of Tablets A and B are shown in Figs. 9 and 10, respectively. In addition, pharmacokinetic parameters were calculated from the plasma levels, as shown in Table 3.

3.3.2. Comparison of pharmacokinetic studies

We compared changes in the plasma level of theophylline after administration of Tablets A and B to five male volun-

Table 2
Pharmacokinetic parameters of theophylline in dogs

Tablet	Subject	C_{max} (μg/mL)	T_{max} (h)	$t_{1/2}$ (h)	$AUC_{0–48}$ (μg h/mL)	$MRT_{0–48}$ (h)	$VRT_{0–48}$ (h^2)
A	1	7.25	2.0	6.98	75.07	9.68	80.04
	2	8.52	4.0	4.89	149.47	14.47	103.03
	3	5.70	2.0	5.98	78.82	10.81	80.78
	4	8.66	4.0	7.28	103.41	10.19	78.65
	5	6.84	8.0	5.66	106.49	10.59	54.81
	6	7.95	4.0	6.89	84.18	9.61	64.93
Mean		7.49	4.0	6.28	99.57	10.89	77.04
S.D.		1.12	2.2	0.92	27.64	1.82	16.38
CV (%)		15.0	54.8	14.7	27.8	16.7	21.3
B	1	5.15	2.0	6.76	67.50	9.74	65.69
	2	8.16	4.0	5.89	168.93	15.92	103.10
	3	4.83	2.0	5.11	58.54	9.90	70.88
	4	7.23	4.0	6.57	80.58	9.45	67.75
	5	5.37	4.0	6.17	52.99	9.04	56.51
	6	10.00	8.0	6.90	146.25	12.96	75.65
Mean		6.79	4.0	6.23	95.80	11.17	73.26
S.D.		2.05	2.2	0.67	49.29	2.72	15.94
CV (%)		30.1	54.8	10.7	51.5	24.3	21.8

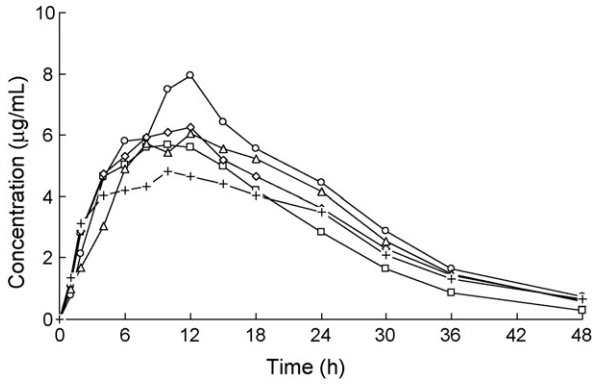

Fig. 9. Plasma theophylline concentrations as a function of time in each human volunteer after oral administration of Tablet A under non-fasting conditions: (◯) 1, (□) 2, (◇) 3, (△) 4, and (+) 5.

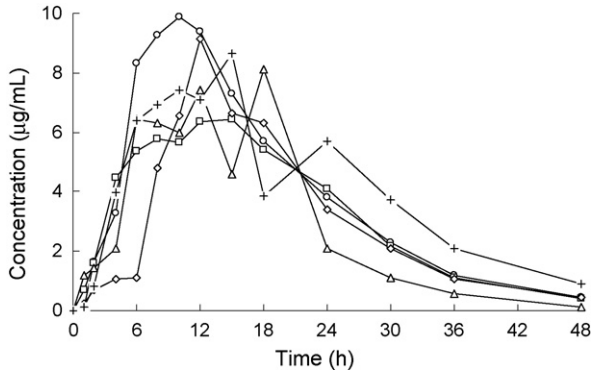

Fig. 10. Plasma theophylline concentrations as a function of time in each human volunteer after oral administration of Tablet B under non-fasting conditions: (◯) 6, (□) 7, (◇) 8, (△) 9, and (+) 5.

teers each. The mean plasma level of theophylline gradually increased to a maximum (6.09 μg/mL) 12 h after administration of Tablet A, but then decreased, with a half-life of 9.10 h. The mean plasma level of theophylline gradually increased to a maximum (7.87 μg/mL) 12 h after administration of Tablet B, but then decreased, with a half-life of 7.76 h. Tablet A showed significantly higher values 1 and 2 h after administration; however, there were no significant differences at the other points.

The values of C_{max}, a pharmacokinetic parameter, were 6.15 ± 1.14 μg/mL and 8.44 ± 1.30 μg/mL after administration of Tablets A and B, respectively. The T_{max} were 11.2 ± 1.1 h and 14.0 ± 3.1 h, respectively. The $t_{1/2}$ were 9.10 ± 1.21 h and 7.76 ± 1.10 h, respectively. The $AUC_{0–24}$ were 109.77 ± 12.89 μg h/mL and 124.48 ± 14.05 μg h/mL, respectively. The $AUC_{0–48}$ were 150.36 ± 19.39 μg h/mL and 163.11 ± 24.28 μg h/mL, respectively. The $MRT_{0–48}$ were 17.69 ± 0.97 h and 17.31 ± 1.57 h, respectively. The $VRT_{0–48}$ were 110.99 ± 9.16 h^2 and 89.75 ± 17.98 h^2, respectively. Tablet B showed a significantly higher C_{max} compared to Tablet A. However, there were no significant differences in the other pharmacokinetic parameters between the two preparations.

Early after administration of Tablet A, the plasma level of theophylline more markedly increased, and an effective plasma level was maintained until 5 h after administration. Then, the plasma level of theophylline was lower than that after administration of Tablet B until 24 h after administration. There were no significant differences between the two preparations more than 24 h after administration. The therapeutic concentration of theophylline ranges from 10 to 20 μg/mL, and side effects such as nausea, vomiting, palpitation, and anorexia have been reported (Weinberger and Bronsky, 1974). The doses of the two preparations employed in this study were below this range. However, at a plasma level ranging from 5 to 20 μg/mL, theophylline exhibits bronchodilating actions in proportion to the plasma level (Mitenko and Ogilvie, 1973). According to a study, at 5 μg/mL or less, theophylline markedly improved clinical symptoms (Maselli et al., 1970). Therefore, Tablet A may reduce side effects by decreasing the maximum plasma level compared to Tablet B.

Table 3
Pharmacokinetic parameters of theophylline in human volunteers

Tablet	Subject	C_{max} (μg/mL)	T_{max} (h)	$t_{1/2}$ (h)	$AUC_{0–24}$ (μg h/mL)	$AUC_{0–48}$ (μg h/mL)	$MRT_{0–48}$ (h)	$VRT_{0–48}$ (h^2)
A	1	7.94	12.0	9.50	129.11	179.00	18.12	110.95
	2	5.67	10.0	7.40	103.50	131.52	16.07	97.83
	3	6.24	12.0	9.50	112.61	153.92	17.57	115.58
	4	6.05	12.0	8.50	109.44	154.32	18.52	108.06
	5	4.83	10.0	10.60	94.19	133.04	18.17	122.52
Mean		6.15	11.2	9.10	109.77	150.36	17.69	110.99
S.D.		1.14	1.1	1.21	12.89	19.39	0.97	9.16
CV (%)		18.5	9.8	13.3	11.7	12.9	5.5	8.3
B	6	9.89	10.0	7.90	146.41	184.93	16.34	90.39
	7	6.42	15.0	7.50	117.52	154.99	17.27	95.26
	8	9.13	12.0	8.20	109.58	144.26	18.32	81.88
	9	8.12	18.0	6.10	120.06	138.78	15.32	66.13
	10	8.66	15.0	9.10	128.83	192.58	19.30	115.09
Mean		8.44	14.0	7.76	124.48	163.11	17.31	89.75
S.D.		1.30	3.1	1.10	14.05	24.28	1.57	17.98
CV (%)		15.5	22.0	14.2	11.3	14.9	9.1	20.0

The pharmacokinetic parameters after administration of Tablets A and B were compared among the subjects. The T_{max} ranged from 10 to 12 h after administration of Tablet A, relatively constant. However, after administration of Tablet B, the values ranged from 10 to 18 h. The CV for T_{max} was 9.8% for Tablet A and 22.0% for Tablet B. After administration of Tablet B, the plasma level of theophylline varied at each point, suggesting that Tablet A shows less marked inter-subject variations. The results were consistent with the results of a pharmacokinetic study in dogs. Therefore, Tablet A may be more useful than Tablet B with respect to pharmacokinetics.

4. Conclusion

We investigated the usefulness of two theophylline preparations, swelling/disintegration-type sustained-release matrix tablets to be administered once a day. We conducted an *in vitro* dissolution test under various test conditions. We administered the two preparations to dogs and humans, and compared sustained-release properties.

(1) The two preparations were not influenced by pH in a dissolution test, suggesting that they do not depend on pH.
(2) In a dissolution test under severe conditions, we employed the bead method. Tablet A was more markedly influenced compared to Tablet B. This may have been because Tablet A was swollen and disintegrated after the start of the test. The influence on Tablet B was less marked than that of agitation intensity when the paddle method was used. The dissolution properties were only slightly influenced when the bead method involving mechanical forces was employed.
(3) The influence of polysorbate 80 as a surfactant was investigated. The two preparations were not influenced by this surfactant. In particular, there was no influence on Tablet B.
(4) We examined the influence of diet in an *in vitro* test. There were no marked changes in the dissolution properties of Tablets A or B, suggesting that diet does not affect these preparations.
(5) In dogs, there were no significant differences in pharmacokinetic parameters between the two preparations. This may have been because intense digestive tract movement in dogs destroyed the matrices of the two preparations, reducing the difference. However, the CV for Tablet B was higher than that for Tablet A, suggesting marked differences. These results suggest that Tablet A is more useful.
(6) In humans, the C_{max}, a pharmacokinetic parameter, after administration of Tablet B was significantly higher than that after administration of Tablet A. However, there were no significant differences in the other pharmacokinetic parameters between the two preparations. We compared the pharmacokinetic data among the subjects. The T_{max} of Tablet A was 10–12 h after administration, relatively constant. However, that of Tablet B was 10–18 h after administration. The CV for T_{max} was 9.8% for Tablet A and 22.0% for Tablet B. After administration of Tablet B, the plasma level of theophylline varied at each point. Based on these results, inter-subject variations after administration of Tablet A may be less marked than those after administration of Tablet B. Therefore, Tablet A may be more useful than Tablet B with respect to pharmacokinetics.

Thus, we found a new sustained-release theophylline matrix tablet (cluster tablets) preparation in which there were no differences in a pharmacokinetic study.

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