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Effect of magnetically controlled gastric residence of sustained release tablets on bioavailability of acetaminophen

Junya Fujimori, Yoshiharu Machida *, Sachiko Tanaka, Tsuneji Nagai

Department of Pharmaceutics, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan

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Abstract

Two types of magnetically responsive sustained release tablets (magnetic tablet) with different drug release rates were prepared using acetaminophen (AAP) as the model drug. The effect of the gastric residence of these magnetic tablets on the bioavailability of AAP was investigated by magnetically controlling the gastric emptying time (GET) in beagle dogs. The area under the plasma concentration-time curve (AUC) of the AAP magnetic tablets after administration with magnet application increased about 2-fold as compared to that during administration without the application of the magnet. The mean residence time (MRT) of AAP magnetic tablets also tended to be prolonged by magnet application. It was suggested from the AAP absorption rate-time profiles obtained using a deconvolution method that the variation in these pharmacokinetic parameters was caused by the delay of 3 h in the GET. Furthermore, the variation in the pharmacokinetic parameters was influenced by the AAP release rate of the magnetic tablets.

Keywords: Magnetic tablet; Acetaminophen; Gastric residence; Gastric emptying time; Gastrointestinal transit time; Bioavailability; Controlled release

1. Introduction

Some drugs are well absorbed from wide regions of the gastrointestinal (GI) tract, however, the majority are mainly absorbed in the small intestine due to its extremely large area for absorption. Therefore, the bioavailability of drugs from oral controlled release systems is influenced by the GI transit time of the systems. The GI transit time of dosage forms has been measured using X-rays (Itoh et al., 1986), a γ-camera (Khosla et al., 1989), and salicylazosulfapyridine (Mizuta et al., 1990). The GI transit time has been found to be variable, since the GET of the dosage forms is affected by factors such as food (Kaniwa et al., 1988) and GI motility (Coupe et al., 1991). The control of the GET of oral controlled release systems might result in more predictable or improved drug bioavailability.

In a previous paper (Fujimori et al., 1994), we described the development of a magnetic tablet which could be retained in the stomach by an externally applied magnetic field. Gastric residence of magnetic tablets could be confirmed in

* Corresponding author.

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beagle dogs by autopsy of the GI tract and measuring the plasma concentration of cinnarizine, an acid-soluble drug. In the present study, AAP and theophylline (TPL) were chosen as the model and control drugs, respectively, because of their good absorptivity and the wide absorption region of TPL in GI tract. Two types of bilayered magnetic tablets of AAP, F (fast release) and S (slow release) tablets with different sustained release properties, were prepared. The effect of gastric residence of the F and S tablets on bioavailability was investigated in beagle dogs under a magnetically controlled GET. Furthermore, the delay of the GET (ΔGET) of the magnetic tablets induced by magnet application was estimated from the rate of absorption of AAP calculated using a deconvolution method.

2. Materials and methods

2.1. Chemicals

Acetaminophen (AAP) and theophylline (TPL) were purchased from Sigma Chemical Co. Ultrafine ferrite (γ-Fe_2O_3, needles of 0.01–0.05 μm diameter and 0.1–0.5 μm length) was kindly supplied by Dainichi Seika Color and Chemicals Mfg Co., Ltd. Hydroxypropyl cellulose-H (HPC), microcrystalline cellulose (MCC), potato starch (PS) and lactose (Lac) were of Japanese Pharmacopeia (JP) XII grade. Ethylene-vinyl acetate copolymer (Evaflex 250®) was purchased from Mitsui Dupont Polychemical Co., Ltd. Diazepam (Cercine® injection), ketamine hydrochloride (Ketalar 50® injection) and tetragastrin potassium iodide (Tetragastrin KI® injection) were purchased from Takeda Chemical Industries, Ltd, Sankyo Co., Ltd and Mect Co., respectively. All other reagents were of special reagent grade.

2.2. Preparation of bilayered magnetic tablets

Table 1 shows the compositions of the bilayered magnetic tablets (6 mm diameter) of AAP and TPL. Each layer containing the drug (drug layer) or ferrite (magnetic layer) was separately prepared by direct compression of the given amount of mixtures at 2000 kg/cm^2 using a Shimadzu hydraulic press. The magnetic layer was coated with 15% chloroform solution of a water-insoluble polymer (ethylene-vinyl acetate copolymer) to prevent its disintegration. After drying, the magnetic layer was stuck to the drug layer with cyanoacrylate-type adhesives. Ordinary tablets (disintegrating tablets) of AAP and TPL (AAP or TPL/PS/MCC = 35:28:7 by wt) were also prepared by direct compression.

Table 1
Composition of bilayered magnetic tablets of acetaminophen and theophylline (mg/tablet)

Material	Tablet type		
	F tablet	S tablet	TPL magnetic tablet
Drug layer			
Acetaminophen	35	35	–
Theophylline	–	–	35
HPC	16.5	35	35
Lactose	18.5	–	–
Magnetic layer			
HPC	21.3	21.3	21.3
Ultrafine ferrite	63.7	63.7	63.7
Total (mg)	155	155	155

2.3. Dissolution test

The in vitro dissolution test was performed using the JP XII paddle method with a Toyama NTR-VS type dissolution tester (100 rpm) and 900 ml of the dissolution medium at 37°C. The first fluid in the JP XII (pH 1.2) was used as the dissolution test medium. In certain studies, the magnetic tablet was taken out of the first fluid at 2 h and the medium was changed to the JP XII second fluid (pH 6.8). 5-ml samples of the solution were withdrawn at appropriate intervals through a Fine Filter F (Ishikawa Seisakusho Co., Ltd) and immediately replaced with an equal volume of the test medium. The concentrations of AAP and TPL in the collected sample solution were spectrophotometrically determined at 244 and 270 nm, respectively, using a Hitachi 200-20 spectrophotometer.

2.4. Absorption study

Three male beagle dogs weighing 9–11 kg and fasted for 15 h prior to drug administration were

used. The interval between each administration was more than 1 week. Tetragastrin (10 μg/kg i.m.) was administered at 20 min prior to and at 40 min after drug administration in order to maintain the gastric pH constant (pH < 2, Yamada et al., 1990). An ordinary tablet or a bilayered magnetic tablet was orally administered with approx. 50 ml of water. The dose was 35 mg for each dog. Absorption studies of all these tablets were carried out under the same conditions according to a method developed in a previous paper (Fujimori et al., 1994) for applying a magnetic field to the stomach of each dog. The dog was fixed into a dog-restraining apparatus (Natsume Seisakusho Co., Ltd) immediately after administration of a tablet. Ketamine hydrochloride (5 mg/kg, i.m.) and diazepam (1 mg/kg, i.m.) were then administered to keep the dogs quiet during the experiment. The administration of diazepam (0.5 mg/kg, i.m.) lasted for 6 h at 1-h intervals after administration of a tablet. In cross-over studies of the gastric residence of the S or F tablet, a magnetic field of 1000–2600 G was applied to the stomach of the beagle dogs for 8 h after the administration of the magnetic tablet.

To determine the absorption rates of drugs from the GI tract, AAP and TPL were intravenously administered at a dose of 35 and 10 mg/dog, respectively. At given intervals, a 2.5 ml blood sample was taken from the cephalic vein of the dogs. The blood samples were centrifuged for 10 min at 3000 rpm. Plasma samples were removed and frozen until analysis.

2.5. Assay for AAP and TPL in plasma

Acetaminophen concentration in plasma was determined using a high-performance liquid chromatographic (HPLC) method. To 0.5 ml of plasma, 0.1 ml of distilled water, 0.1 ml of 2-acetaminophenol aqueous solution (35 μg/ml) as an internal standard, and 5 ml of ethyl acetate were added. After shaking for 10 min, the organic layer was taken and evaporated under N_2 gas. The residue was dissolved in 100 μl of the mobile phase described below and an aliquot was used for analysis. The analysis was performed using a μ-Bondapack C18 column (3.9 × 300 mm, 10 μm particle size; Waters) with a mobile phase of methanol-acetonitrile-water (6:6:88, v/v) and a flow rate of 1.5 ml/min. Acetaminophen was detected by measuring the absorbance at 254 nm.

Theophylline concentration in plasma was determined according to the HPLC method reported by Ishizaki et al. (1979). An inertsil ODS-2 column (4.6 × 250 mm, 5 μm particle size; GL Sciences) was used for the analysis.

2.6. Pharmacokinetic analysis

The peak plasma concentration (C_{max}) and the time taken to attain the peak concentration (T_{max}) were directly determined from the plasma concentration-time curves. The area under the plasma concentration-time curve from time zero to infinity after administration ($AUC_{0-\infty}$) and the mean residence time (MRT) were calculated according to the linear trapezoidal rule (Yamaoka, 1982). The absorption rates of the drug were calculated from intravenous (as a weighting function) and oral administration data (as an output function) using a deconvolution program (Nankoudo Co., Ltd) developed by Yamaoka (1982).

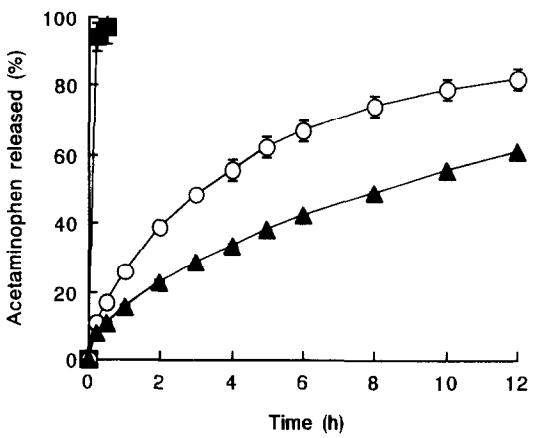

Fig. 1. Release profiles of acetaminophen from AAP ordinary tablets, F tablets and S tablets in JP XII 1st fluid (pH 1.2). (■) AAP ordinary tablets (AAP/PS/MCC = 5:4:1); (○) F tablets (AAP/Lac/HPC = 100:53:47); (▲) S tablets (AAP/HPC = 1:1). Each point represents the mean ± S.D. ($n = 3$).

2.7. Statistical analysis

Pharmacokinetic parameters were statistically subjected to Student's t-test.

3. Results and discussion

3.1. In vitro dissolution studies

Fig. 1 shows the release profiles of AAP from ordinary tablets, F tablets and S tablets in the JP XII 1st fluid (pH 1.2). The release of AAP from ordinary tablets reached 100% within 15 min, however, the F and S tablets showed different sustained release profiles over 12 h. The time taken to release 50% of AAP for the F (fast release) and S (slow release) tablets was about 3 and 7 h, respectively. To compare the absorption of AAP from the GI tract with that of TPL, TPL magnetic tablets having the same release rate and tablet size as the S tablets were prepared. Fig. 2 demonstrates the release profiles of AAP and TPL from S tablets and TPL magnetic tablets. The release properties of the two magnetic tablets did not significantly differ, although the dissolution test medium was changed from the first fluid to the second fluid (pH 6.8) on considering the GI transit of tablets.

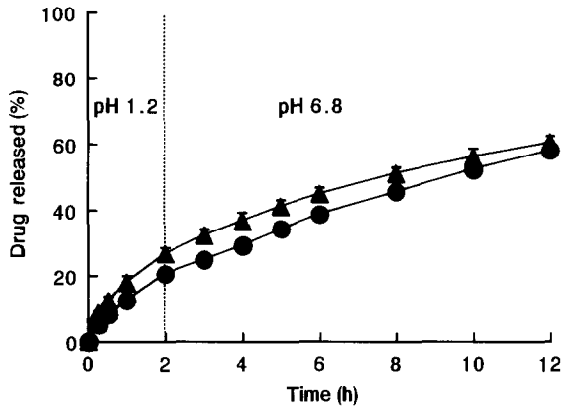

Fig. 2. Release profiles of acetaminophen and theophylline from magnetic tablets in JP XII 1st fluid (pH 1.2) and 2nd fluid (pH 6.8). (▲) S tablets (AAP/HPC = 1:1); (●) TPL magnetic tablets (TPL/HPC = 1:1). Each point represents the mean ± S.D. ($n = 3$).

3.2. Effect of drug release rate on pharmacokinetic parameters in AAP formulations

Fig. 3 and 4 show the plasma drug concentration-time profiles after oral administration of different formulations of AAP and TPL, respectively. The pharmacokinetic parameters obtained are summarized in Table 2. In the case of AAP formulations, the C_{max} values were reduced and

Table 2
Pharmacokinetic parameters for acetaminophen and theophylline formulations with different drug release rates

Formulation	T_{max} (h)	C_{max} (ng/ml)	MRT (h)	$AUC_{0-\infty}$ (ng h ml^{-1})	BA_r (%) [b]
Acetaminophen					
Ordinary tablets	0.7	1321.4	1.4	1846.1	–
	±0.2	±173.0	±0.2	±252.1	
F tablets	0.7	296.5 [a]	2.9 [a]	1066.4 [a]	57.9
	±0.2	±55.0	±0.4	±143.3	±3.7
S tablets	1.0	160.3 [a]	3.8 [a]	754.2 [a]	42.6
	±0.5	±4.8	±0.1	±56.1	±7.0
Theophylline					
Ordinary tablets	0.7	2989.8	8.2	27358.5	–
	±0.2	±162.5	±0.9	±2132.0	
TPL magnetic	7.3 [a]	1268.5 [a]	15.5	19733.1	71.6
tablets	±0.9	±78.4	±4.1	±2967.1	±7.8

Each value represents the mean ± S.E. of three dogs.
[a] $p < 0.05$, compared to the values of the corresponding ordinary tablets.
[b] Relative bioavailability against the corresponding ordinary tablets.

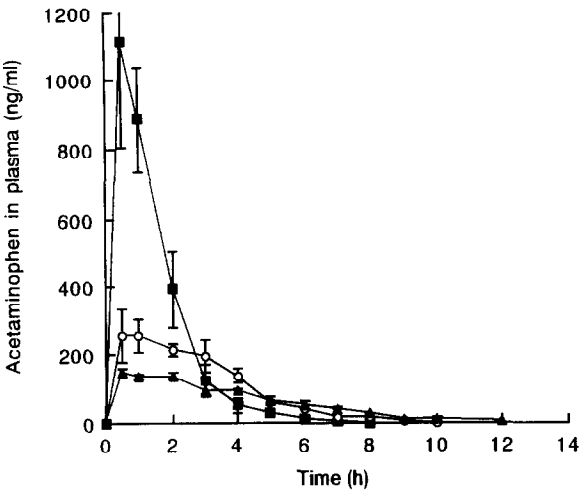

Fig. 3. Plasma concentration-time profiles of acetaminophen after oral administration of AAP ordinary tablets, F tablets and S tablets. (■) AAP ordinary tablets; (○) F tablets; (▲) S tablets. Each point represents the mean ± S.E. ($n = 3$).

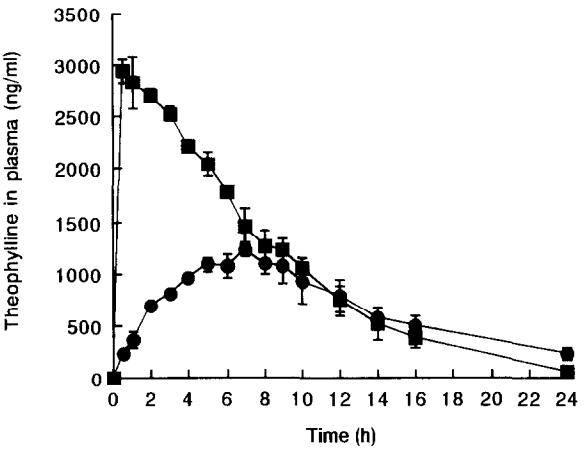

Fig. 4. Plasma concentration-time profiles of theophylline after oral administration of TPL ordinary tablets and TPL magnetic tablets. (■) TPL ordinary tablets; (●) TPL magnetic tablets. Each point represents the mean ± S.E. ($n = 3$).

the MRT values were prolonged with decrease in the in vitro release rate of AAP from the tablets. The $AUC_{0-\infty}$ values also tended to be reduced with decrease in the release rate. In particular, the relative bioavailability (BA_r) of the S tablets, calculated from the $AUC_{0-\infty}$ values vs the ordinary tablets, decreased to 42.6%. Such a decrease in the BA_r might be a disadvantage when considering the development of AAP controlled release systems. In the case of TPL formulations, C_{max} and $AUC_{0-\infty}$ values indicated behavior similar to those of AAP formulations. However, the BA_r value for TPL magnetic tablets was significantly greater than that of the S tablets.

In order to consider the difference in BAr between the S tablets and TPL magnetic tablets, the absorption rate of AAP and TPL was calculated by the deconvolution method. The results are shown in Fig. 5. The GI transit rate of the S tablets should be almost the same as that of TPL magnetic tablets, since these tablets have the same size. In addition, these tablets show the same drug release rate at both pH 1.2 and pH 6.8. The GI absorption of AAP and TPL is known to follow first-order kinetics (Rovei et al., 1982; Borin and Ayres, 1989). Therefore, Fig. 5 should show a difference between the absorption rate constants of AAP and TPL in the same part of the GI tract. In the upper part of the small intestine, the absorption rate constants of AAP and TPL were comparable. Considering the excellent absorptivity of TPL in the absorption region, the decrease in BA_r of the S tablets would not be due to the first-pass effect of AAP. However, the absorption rate constant of AAP was lower than that of TPL in the lower part of the GI tract. A marked decrease in BA_r for the S

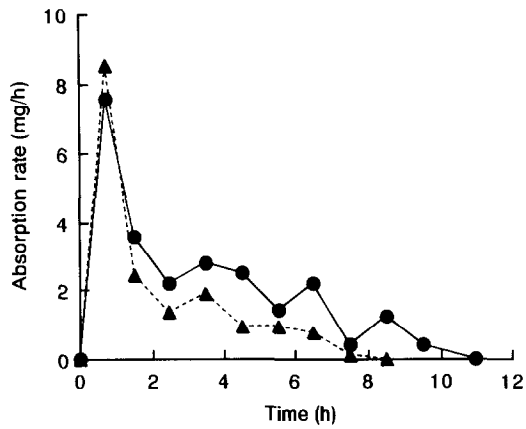

Fig. 5. Absorption rate-time profiles of acetaminophen and theophylline after oral administration of S tablets and TPL magnetic tablets. (●) TPL magnetic tablets; (▲) S tablets.

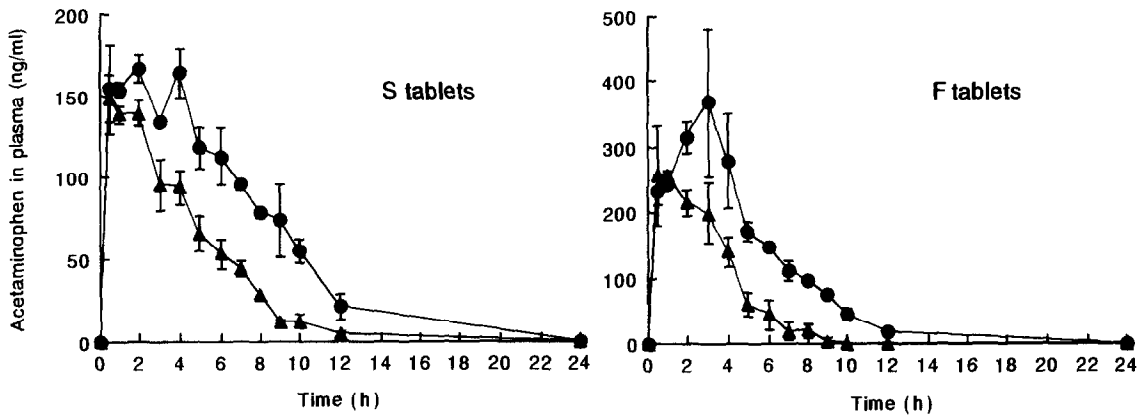

Fig. 6. Plasma concentration-time profiles of acetaminophen after oral administration of S and F tablets. (●) With application of magnet for 8 h; (▲) without magnet. Each point represents the mean ± S.E. ($n = 3$).

tablets may be attributed to the limited absorption region of AAP.

In conclusion, the lowering of BA_r in AAP controlled release systems might be due to a decrease in AAP released in the absorption region of the GI tract.

3.3. Effect of gastric residence on bioavailability of AAP magnetic tablets

In order to investigate the effect of gastric residence of AAP magnetic tablets on drug bioavailability, a permanent magnet (neodymium-iron-boron magnet) was applied to the stomach of beagle dogs for 8 h after administration of the magnetic tablets. Fig. 6 displays the plasma concentration profiles of AAP following oral administration of the S and F tablets to beagle dogs with or without magnet application. In both magnetic tablets, the AAP plasma concentration was apparently sustained by the application of the magnet. These observations suggest that the GET of the magnetic tablets was prolonged by an externally applied magnetic field.

Fig. 7 shows the effect of magnetic application on the absolute bioavailability (BA) of the S and F tablets. Detailed values of the pharmacokinetic parameters are summarized in Table 3. Magnetic application did not affect the T_{max} and C_{max} values of the S and F tablets. However, the MRT values of these magnetic tablets tended to be prolonged by magnet application. This result may be attributed to the mean absorption time prolonged by the delay of GET of the magnetic tablets. The $AUC_{0-\infty}$ and BA values of the S and F tablets administered with magnet application

Table 3
Effect of magnetic application on pharmacokinetic parameters of acetaminophen after oral administration of S and F tablets

Parameter	S tablets		F tablets	
	Without magnet	With magnet (8 h)	Without magnet	With magnet (8 h)
T_{max} (h)	1.0 ± 0.5	1.0 ± 0.5	0.7 ± 0.2	2.3 ± 0.3
C_{max} (ng/ml)	160.3 ± 4.8	181.8 ± 1.4	296.5 ± 55.0	407.4 ± 93.7
MRT (h)	3.8 ± 0.1	6.6 ± 1.0	2.9 ± 0.4	4.3 ± 0.2
$AUC_{0-\infty}$ (ng h ml^{-1})	754.2 ± 56.1	1455.3 ± 221.9 [a]	1066.4 ± 143.3	1980.1 ± 161.9 [a]
Absolute bioavailability (%)	34.3 ± 3.2	65.5 ± 1.7 [a]	47.8 ± 4.4	89.6 ± 6.7 [a]

Each value represents the mean ± S.E. of three dogs.
[a] $p < 0.05$, compared to the values of the corresponding magnetic tablet without application of magnet.

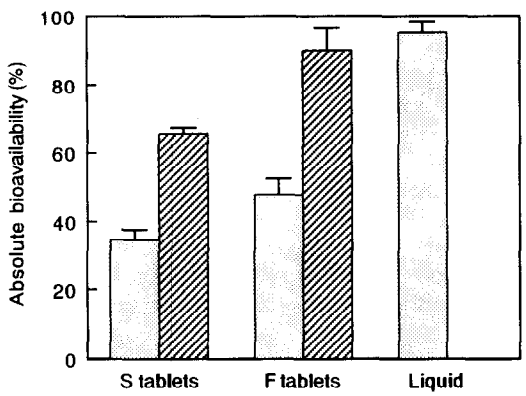

Fig. 7. Effect of magnet application on absolute bioavailability after oral administration of S and F tablets. (▨) Without magnet; (▨) with application of magnet for 8 h. Each value represents the mean ± S.E. ($n = 3$).

increased about 2-fold as compared to those during administration without magnet application. Such increases in $AUC_{0-\infty}$ and BA indicate that the amount of AAP released in the absorption region is increased by the delay of GET of the magnetic tablets.

3.4. Estimation of delay of GET for AAP magnetic tablets using deconvolution method

The delay of GET (ΔGET) induced by magnet application for the S and F tablets was estimated from the AAP absorption rate-time profiles based on the following theory. Ordinary drugs are well absorbed from the small intestine and poorly absorbed from the lower part of the GI tract. Therefore, the end of the major absorption region (point E) which differs with drugs might exist in the GI tract. Once a sustained release tablet passes beyond point E, any further drug release may not contribute to absorption. Accordingly, as the drug absorption rate becomes zero when a tablet reaches point E, the time required to reach point E (T_E) can be estimated from the drug absorption rate-time profiles obtained using the deconvolution method. T_E is equal to the sum of the GET and the transit time from the pylorus to point E. Davis et al. (1984, 1986) reported that the intestinal transit time (i.e., transit time from the pylorus to point E) is constant and independent of dosage forms or feeding state. Therefore, an increase in T_E for a tablet indicates ΔGET. This theory should be applied only when the amount of drug released from the tablet does not reach 100% before it arrives at point E.

In order to confirm whether or not the magnetic tablets passed point E with unreleased AAP, AAP liquids (35 mg/dog) were orally administered to the beagle dogs. As shown in Fig. 7, the BA value of the liquids was greater than that of the S and F tablets administered with or without magnet application. It could be concluded from this result that these magnetic tablets passed point E with unreleased AAP even in the case of magnet application. Fig. 8 demonstrates the AAP

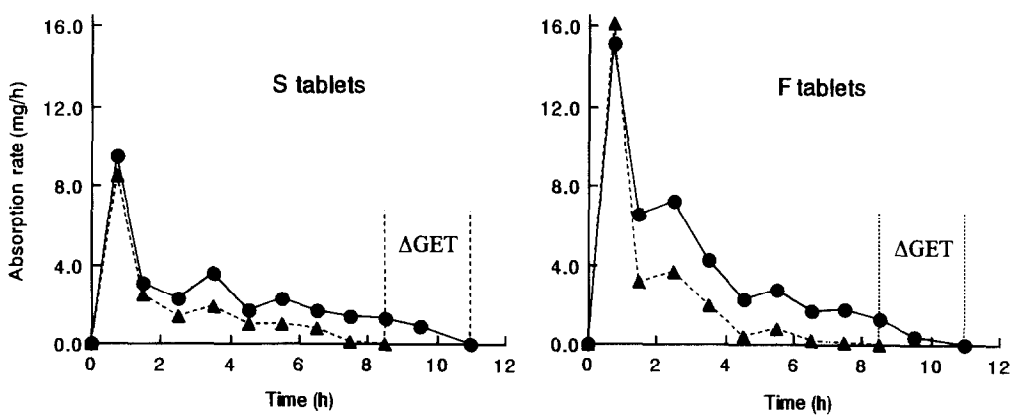

Fig. 8. Absorption rate-time profiles of acetaminophen after oral administration of S and F tablets. (●) With application of magnet for 8 h; (▲) without magnet.

Table 4
Variation in MRT and AUC of acetaminophen magnetic tablets caused by delay of gastric emptying time

Formulation	ΔGET (h)	ΔMRT (h)	ΔAUC (ng h ml^{-1})
S tablets	3.0±0.6	2.8±1.0	701.0± 93.0
F tablets	3.0±1.0	1.4±0.6	913.7±210.6

Each value represents the mean±S.E. of three dogs.

absorption rate-time profiles after oral administration of the S and F tablets to beagle dogs with and without magnet application. In both magnetic tablets, the peak absorption rate was similar regardless of magnet application, however, T_E (when the absorption rate becomes $< 1\%$ of the peak) was significantly prolonged by magnet application. This increase in T_E value can be attributed to a ΔGET of about 3 h in both magnetic tablets.

Table 4 shows the variation in MRT (ΔMRT) and AUC (ΔAUC) of AAP magnetic tablets as a result of ΔGET. Since ΔGET was the same in both tablets, the ΔMRT and ΔAUC values can be compared between the S and F tablets. ΔMRT of the S tablets was significantly longer than that of the F tablets. This may be attributed to a difference in the mean dissolution time of the S and F tablets. On the other hand, ΔAUC tended to be greater in the F tablets than in the S tablets. This may be due to the fact that the amount of AAP released from the F tablets during the residence in the stomach was greater than that from the S tablets. The AUC and MRT values may be more affected by gastric residence of the sustained release tablets with a rapid drug release rate and a slow drug release rate, respectively.

4. Conclusions

A decrease in BA for AAP controlled release systems was significantly improved by a delayed GET of the systems and the MRT was also prolonged. A variation in these pharmacokinetic parameters caused by a delay of GET was influenced by the drug release rate of the systems. Based on these results, we can conclude that the development of more efficient oral controlled release systems should be achieved by the optimum combination of GET control and the drug release rate of the systems.

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