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A new index, the core erosion ratio, of compression-coated timed-release tablets predicts the bioavailability of acetaminophen

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Abstract

Although compression-coated tablets are a commonly used timed-release drug delivery technology, their utility is often limited by poor bioavailability. To try to improve the bioavailability of these tablets, the effect of their core composition of compression-coated tablet on in vivo pharmacokinetics was investigated. First, the extent of mass reduction of cores in different compression-coated tablet core formulations was used to establish a new index, the core erosion ratio. The data show that adding excipients with high water solubility to the core results in a greater core erosion ratio. Next, to elucidate the effect of core erosion ratio on in vivo acetaminophen (AAP) release, three compression-coated tablet formulations with similar in vitro AAP release profiles but different core erosion ratios were administered to four fasted dogs. The time for first appearance (TFA) of AAP in plasma did not differ significantly among formulations, indicating that the in vivo lag time was the same for all formulations. In separate experiments, necroscopy revealed that 3 h after oral administration, the tablets were located in the ileum and colon and that all three formulations had identical GI transit times. However, the area under the AAP plasma concentration–time curve was greater in dogs given formulations with larger core erosion ratios. These results suggest that a formulation with a large core erosion ratio can significantly increase in vivo drug release from compression-coated tablets, leading to increased drug absorption from the lower GI tract.

Keywords: Compression-coated tablets; Timed-release formulation; Dogs; Acetaminophen; Core erosion ratio

1. Introduction

Timed-release formulations are designed to release a drug at a predetermined time (the lag time) after administration. Orally administered timed-release dosage forms have been widely investigated for use in chronopharmacologic therapy, in site-specific drug delivery, in peptide drug absorption enhancement, and in avoiding pharmacokinetic drug–drug interactions (Cutler et al., 1995; Niwa et al., 1995; Matsuo et al., 1996; Sawada et al., 2003). However, timed-release dosage forms often have poor bioavailability compared to immediate-release conventional dosage forms. This effect is thought to result from poor dissolution and absorption of the drug in the lower gastrointestinal (GI) tract, most commonly the ileum and the colon. These are the sites that many controlled-release dosage forms reach

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2–3 h after oral administration to dogs and 5–8 h after administration to humans (Sako et al., 1996a; Davis et al., 1986). Indeed, results from a pharmacokinetic study on a capsule-shaped timed-release dofetilide formulation indicate that such formulations have 57% lower bioavailability when drug release occurs in the colon than that of the corresponding oral solution (Stevens et al., 2002). This phenomenon might result from insufficient water in the colon to dissolve the drug rapidly, and the viscosity of lower GI contents that might restrict drug dispersion in the colon (Takaya et al., 1998; Stevens et al., 2002).

Several timed-release technologies have been described. These include use of a rupturable coating that surrounds multiple pellets loaded with the drug (Ueda et al., 1994); a compression-coated soluble barrier that erodes, surrounding a single unit-core tablet containing the drug (Conte et al., 1993; Gazzaniga et al., 1994); and a swellable hydrogel plug which dislodges when swollen, set into a water-insoluble capsule body filled with the drug (Wilding et al., 1992; Krőgel and Bodmeier, 1998). Of these formulations, compression-coated tablets are among the simplest to manufacture. Compression-coated tablets are composed of an inner core that contains an active pharmaceutical ingredient surrounded by an outer layer that slowly dissolves or disintegrates to make a lag time of drug release.

It has been previously reported that reduced drug release from sustained-release hydrogel-forming tablets in the colon is the main reason for decreased absorption of acetaminophen (AAP) from the colon (Sako et al., 1996b). However, the in vivo drug release of such tablets in the colon was improved by enhancing their gelation rate (Sako et al., 1996a). In the case of compression-coated timed-release formulations that contain a drug only in the core of the formulation, little is known about how the characteristics of the core affect drug release. Consequently, this study tested the following hypothesis: if the core of a compression-coated formulation absorbs water during the lag time, time-controlled drug release and better dissolution can be obtained in the lower GI tract where little water is available. In vitro formulation studies were conducted to find a formulation that enhances water penetration into the core of a compression-coated tablet, and an in vivo pharmacokinetic study on several of these new timed-release formulations was conducted in dogs to determine the effect of core composition on their bioavailability.

2. Materials and methods

2.1. Materials

AAP was purchased from Yoshitomi Pharmaceutical Industries Ltd. (Osaka, Japan). Polyox WSR 303, a polyethylene oxide (PEO) with an average molecular weight of 7 million, was purchased from Dow Chemical (Piscataway, NJ). Macrogol 6000, a polyethylene glycol (PEG) with an average molecular weight between 7300 and 9300, was purchased from Sanyo Chemical Industries (Kyoto, Japan). Dextran Blue 2000 was purchased from Amersham Pharmacia Biotech AB (Uppsala, Sweden) and was used after being ground to a fine powder in an agate mortar and pestle. Other reagents used were of analytical reagent grade.

2.2. In vitro experiments

2.2.1. Preparation of compression-coated tablets

A single press tableting machine was used to prepare the core tablets by direct compression using concaved punches of 6.5 mm diameter and radius of curvature of 7.8 mm. Then, compression-coated tablets were prepared by placing 50% of the outer layer powder mixture in the die, manually centering the previously prepared tablet cores on the powder in the die, and loading the remaining 50% of the outer layer powder mixture into the die. The contents were then compressed using a single press tableting machine using concaved punches of 9.5 mm diameter and radius of curvature of 11.4 mm. The composition of each formulation are shown in the Tables 1 and 2.

2.2.2. Water permeability tests

Three compression-coated tablets, LL, LP, and PP (Table 1) were used to evaluate the extent of water penetration into the tablets. These formulations contained 0.2 mg of Dextran Blue 2000 in the core to aid easy recognition of water penetration. Each tablet was separately immersed in water kept at 37 °C for

Table 1
Formulation of compression-coated tablets used in in vitro water permeability test

	Formulation code		
	LL	LP	PP
Core part			
Lactose	150	150	–
PEG	–	–	150
Dextran Blue 2000	0.2	0.2	0.2
Subtotal mass (mg)	150.2	150.2	150.2
Thickness (mm)	3.8	3.8	4.3
Diameter (mm)	6.5	6.5	6.5
Outer layer			
PEO	125	125	125
Lactose	125	–	–
PEG	–	125	125
Total mass (mg)	400.2	400.2	400.2
Thickness (mm)	5.3	5.5	5.7
Diameter (mm)	9.5	9.5	9.5

3 h. The tablets were then removed from the medium and allowed to stand for 2 h. Visual observation of the color change and the condition of the core were used to evaluate the extent of water penetration.

2.2.3. In vitro core erosion test

Compression-coated tablets were separately immersed in the Japanese Pharmacopoeia XIII (JP) Disintegration test second fluid (pH 6.8) at 37 °C for 3 h. After the tablets were removed from the medium, the gelated portion of the outer layer and the dissolved or gelated portion of each core tablet were carefully removed to obtain the non-eroded residual core. The dry mass of each non-eroded residual core (W_{core}) was measured after drying for 20 h at 40 °C. The initial mass of each core tablet (W_{ini}) and the mass of each non-eroded core (W_{core}) were used to calculate the core erosion ratio as follows:

$$\text{Core erosion ratio (\%)} = \left(1 - \frac{W_{core}}{W_{ini}}\right) \times 100 \qquad (1)$$

2.2.4. In vitro AAP release test

The second method (paddle method) of JP Dissolution test was used to determine the amount of AAP released from compression-coated tablets, TR-A, TR-B, and TR-F, in vitro. The paddle rotation speed was set to 200 rpm. A previous study demonstrated that in vivo drug release from hydrogel matrix tablets in fasted dogs was close to its in vitro release pattern by the pad-

Table 2
Formulation of compression-coated tablets used in in vitro and in vivo test

	Formulation code					
	TR-A	TR-B	TR-C	TR-D	TR-E	TR-F
Core part						
Acetaminophen	50	50	50	50	50	50
PEG	75	–	–	–	–	–
Sucrose	–	75	–	–	–	–
PVP K30	–		75	–	–	–
Citric acid	–		–	75	–	–
Mannitol	–	–	–	–	75	–
Lactose	–	–	–	–	–	75
PEO	25	25	25	25	25	25
Sub total mass (mg)	150	150	150	150	150	150
Thickness (mm)	4.4	4.2	4.4	4.2	4.3	4.3
Diameter (mm)	6.5	6.5	6.5	6.5	6.5	6.5
Outer layer						
PEO	125	125	125	125	125	125
PEG	125	125	125	125	125	125
Total mass (mg)	400	400	400	400	400	400
Thickness (mm)	5.7	5.6	5.9	5.6	5.6	5.6
Diameter (mm)	9.5	9.5	9.5	9.5	9.5	9.5

dle method at 200 rpm (Sako et al., 1996b). The paddle rotation speed of 200 rpm was therefore adopted for the in vitro drug release test. The test medium was 500 ml of the second fluid (pH 6.8) for the JP Disintegration test. Samples were taken at appropriate intervals, and the amount of dissolved AAP was determined spectrophotometrically at 280 nm. The lag time of drug release was determined from the intersection of the release profile regression line formed from data taken between 20 and 80% release with the time axis.

2.3. In vivo experiments

All experiments using beagle dogs were approved by the Animal Care and Use Committee of Novel Pharmaceutical Laboratories in Yamanouchi Pharmaceutical Co., Ltd. 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.

2.3.1. Preparation of test tablets

The compression-coated tablets were prepared as described in Section 2.2.1 and Table 2.

2.3.2. Pharmacokinetic test

Four male beagle dogs weighing 11.4–13.6 kg were fasted for 20 h before administration. After administration, they were allowed free access to water but food was withheld until the last blood sample had been taken. Timed-release compression-coated tablets, TR-A, TR-B, and TR-F, containing 50 mg of AAP were separately administered orally with 30 ml of water. A minimum 1-week washout period was provided between each administration. Blood samples were collected at 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 h after administration. Plasma samples were immediately separated and stored frozen at −20 °C until assay.

2.3.3. Assay procedure to determine AAP plasma concentration

The extraction procedure and HPLC assay method for AAP were performed according to a previously reported procedure (Ameer et al., 1981). An aqueous solution of 60 μg/ml 2-acetaminophenol was prepared for use as the internal standard. For each plasma sample, 0.1 ml of the internal standard solution and 5 ml of ethyl acetate were sequentially added to 0.5 ml of plasma in a test tube. The tube was shaken for 10 min, and centrifuged for 5 min at 2000 rpm. The upper organic layer was transferred to a clean test tube, and then evaporated to dryness. The dried residue was dissolved in 0.1 ml of an HPLC mobile phase consisting of water–acetonitrile–methanol (88:6:6, v/v/v). The HPLC separation was performed on an octadecylsilane column (Nucleosil, 150 mm length × 4.6 mm diameter, 5 μm; Chemco Scientific Co., Ltd.; Osaka, Japan) at ambient temperature. AAP extracted from plasma was detected by ultraviolet (UV) spectroscopy at 254 nm.

2.3.4. Analysis of pharmacokinetic data

The maximum plasma level (C_{max}) was determined according to a standard procedure. The linear trapezoidal method was used to calculate the area under the plasma concentration versus time curve (AUC). The time for first appearance (TFA) of AAP in plasma was defined as the blood sample collection time when AAP was first detected in plasma. The paired *t*-test was used to test for differences between the formulations. To test for a correlation between the core erosion ratio and the C_{max} or AUC values, a 5% significance level was chosen and Spearman's rank correlation coefficients were then calculated. The statistical software package SAS (version 8.2; SAS Institute Inc.; Cary, NC) was used to analyze the data.

2.3.5. Necroscopy study

Two male beagle dogs weighing 11.4 and 12.0 kg were fasted for 20 h before administration; the dogs were allowed free access to water during this time. In order to distinguish among the compression-coated tablets in the GI tract, the core tablet of TR-A, TR-B, and TR-F used in this study was labeled with 0.2 mg erythrosine, indigo carmine, and naphthol yellow as a coloring agent, respectively. One TR-A, one TR-B, and one TR-F (Table 2) tablet were simultaneously administered with 30 ml water to each of the two dogs. Three hours after oral administration, the dogs were sacrificed, the whole GI tract of each dog was removed and opened, and the location of each tablet was determined. For analysis, the small intestine was divided into five portions.

3. Results and discussion

3.1. Water-soluble excipients increase tablet water absorption

Three different compression-coated tablet formulations, LL, LP, and PP, were prepared to study what effect water-soluble excipients in the outer layer and the core have on water penetration into the core (Table 1). Lactose was used as an excipient with low water solubility, and PEG was used as an excipient with high water solubility. Fig. 1 shows the significant difference in water penetration observed among the three formulations. For formulation LL, the surface color of the core did not change after immersion in water for 3 h, indicating that the LL outer layer did not completely gelate and water did not reach the core. In contrast, the outer layer of the LP and PP formulations changed to a clear gel and the core color changed to blue after 3 h of immersion, indicating that water reached the core during immersion. Although the outer layer of formulation LP had gelated during the 3 h immersion, the shape of the core had not changed significantly after the 2-h standing period. In contrast, the PP core seemed to be well dissolved after the 2-h standing period. These findings show that more water penetrates into the core of PP tablets than into the core of LP tablets even though their outer layer formulations are the same. This effect is thought to be caused by the presence of PEG in both the outer layer and the core. Previous research indicated that water-soluble fillers such as PEG enhance the gelation rate of controlled-release AAP tablets containing polyethylene oxide (PEO) (Sako et al., 1996a). Therefore, the addition of a water-soluble excipient such as PEG to both the outer layer and the tablet core appears to enhance water penetration into the core of compression-coated tablets. Based on these results, PEO–PEG mixture was selected as the outer layer for subsequent experiments.

3.2. Highly soluble core excipients increase the core erosion ratio

A new method, the core erosion test, was devised to evaluate qualitatively the extent of water penetration into the core of compression-coated tablets. Using this test, the ratio of the amount of core into which water penetrates to the intact core can be obtained. The effect of excipients in the tablet core on the core erosion ratio was then investigated. Six commonly used pharmaceutical excipients with different water solubilities were added to a core containing 50 mg of AAP. The formulations are shown in Table 2. The results show that more than 50% of the core erosion ratio were observed when PEG, citric acid, PVP K30, or sucrose were included in the core (Table 3). Al-

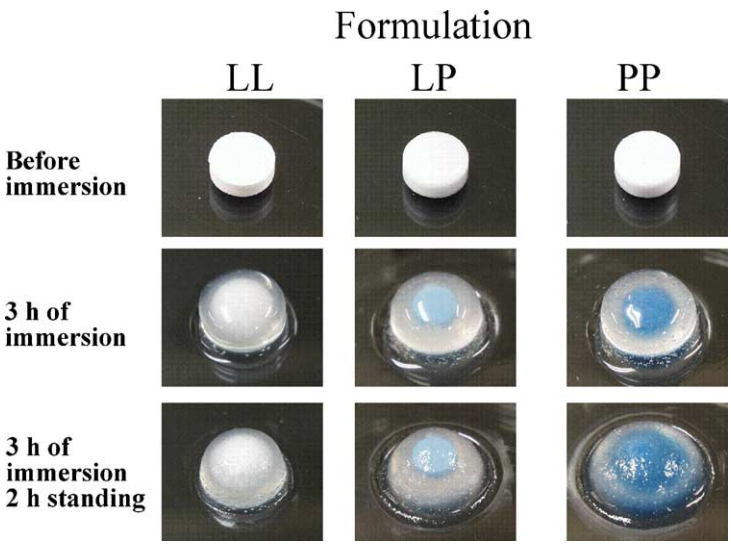

Fig. 1. Photographs showing the change in compression-coated tablets immersed in water. Please see Table 1 for formulation details.

Table 3
Effect of core tablet excipients on in vitro core erosion ratios

Formulation code	Excipient	Water required for 1 g of solute (ml)	Core erosion ratio (%)[a]
TR-A	PEG 6000	<1	88.2 ± 0.7
TR-B	Sucrose	<1	50.9 ± 6.0
TR-C	PVP K30	<l	60.5 ± 0.9
TR-D	Citric acid	<1	82.7 ± 3.5
TR-E	Mannitol	<6	37.5 ± 6.0
TR-F	Lactose	<8	24.6 ± 1.3

[a] Data represent the mean ± S.D. of three experiments.

though the water solubility of sucrose and PVP K30 are almost the same as PEG, the core erosion ratio of the TR-B formulation and TR-C formulation were 37 and 28% less than that of TR-A formulation. It is thought that the highly water-soluble excipients dissolve to enhance water penetration into the formulation. This explanation agrees with results from studies on the gelation index of controlled-release monolithic hydrogel-forming tablets; the index increases when these tablets contain highly water-soluble excipients (Sako et al., 1996a). However, because other factors besides water-solubility of core excipients might serve to increase the core erosion ratio of compression-coated tablets, the additional studies will be required to optimize such formulations.

To better characterize the in vitro and in vivo performance of these formulations, three tablets with different core erosion ratios, TR-A, TR-B, and TR-F, were used in subsequent experiments. Fig. 2 shows the in vitro dissolution profiles of AAP from these compression-coated tablets in the JP second fluid (pH 6.8). All three formulations showed a lag time before AAP dissolution began, indicating that compression-coated tablets using PEO and PEG as an outer layer function as timed-release formulations. The lag time before AAP release from each tablet was 3.4 h for TR-A, 3.5 h for TR-B, and 3.6 h for TR-F; these results are statistically the same. The AAP release rates after the lag time did not differ markedly among the formulations (Fig. 2). These results suggest that the lag time before AAP release from compression-coated tablets does not change when the outer layer consists of the same mixture, and indicate that the dissolution profile after the lag time is not significantly affected by different excipients in the core.

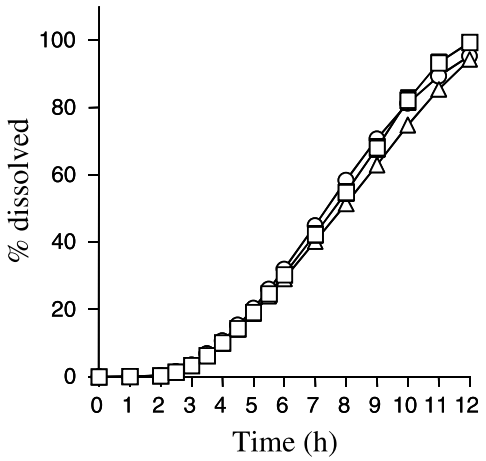

Fig. 2. In vitro dissolution profiles of AAP from TR-A (open square), TR-B (open circle), and TR-F (open triangle) using the paddle method at a rotation speed of 200 rpm in the second fluid (pH 6.8) for the JP Disintegration test. Each point represents the mean ± S.D. of three experiments. For each data point, the error range lies within the space occupied by the symbol.

3.3. Relationship between core erosion ratio and in vivo performance in dogs

In order to investigate what effect the core erosion ratio of compression-coated tablets has on in vivo AAP release properties, three compression-coated tablet formulations with similar in vitro dissolution profiles but different core erosion ratios, TR-A, TR-B, and TR-F (Table 2), were separately administered to fasted dogs. Fig. 3 shows mean plasma levels of AAP after oral administration of compression-coated tablets to fasted dogs. The resulting pharmacokinetic parameters of these formulations are shown in Table 4. The TFA of AAP in plasma, which are indicators of

Table 4
Pharmacokinetics of AAP after oral administration of compression-coated tablets to fasted dogs[a]

Formulation code	AUC (μg h/ml)	C_{max} (μg/ml)	TFA[b] (h)
TR-A	1.4 ± 0.5	0.40 ± 0.25	2.0 ± 0.8
TR-B	1.1 ± 0.5*	0.23 ± 0.11	4.0 ± 1.6
TR-F	0.4 ± 0.2*	0.07 ± 0.02	3.0 ± 0.8

[a] Data represent the mean ± S.D. from four dogs.
[b] Time for first appearance in plasma.
* Significantly different from TR-A ($P < 0.01$).

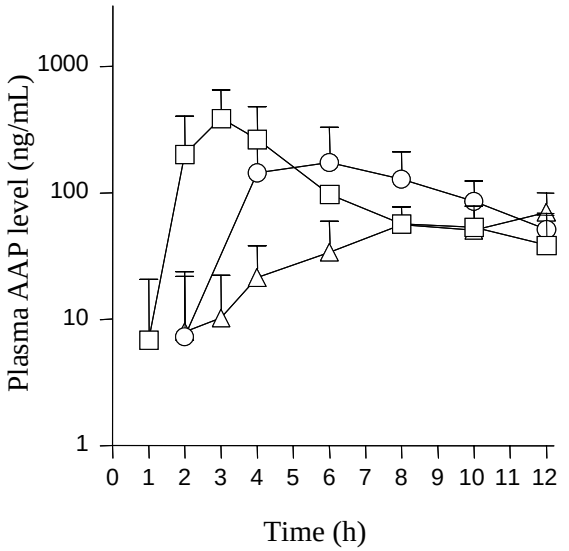

Fig. 3. Plasma levels of AAP after oral administration of TR-A (open square), TR-B (open circle), and TR-F (open triangle) to four fasted dogs. Each point represents the mean ± S.D. of four dogs.

in vivo lag time, was 2.0 ± 0.8 h for TR-A, 4.0 ± 1.6 h for TR-B, and 3.0 ± 0.8 h for TR-F. Since AAP is rapidly absorbed from the intestine regardless of the in vivo release site, the existence of TFA demonstrates that AAP release from compression-coated tablets started only after a lag time in the GI tract. There was no statistically significant difference in TFA values among the three formulations (Table 4), though it seems from the plasma level profiles that the lag time for TR-A is shorter than other two formulations. Similarly, the necroscopy results from dogs sacrificed 3 h after simultaneous oral administration of all three formulations show that these formulations were located in the final fifth portion of the small intestine (ileum) or in the colon (Table 5); these results show the GI transit time of each of these tablets was approximately the same in both dogs. From the visual evaluation, the outer layer of each tablet was completely gelled, and the core tablet was colored by water penetration into the formulation in the ileum of Dog A, while the outer layer of each tablet was already broken in the colon of Dog B. Therefore, it is thought that AAP was released from these formulations in, then absorbed mainly from the ileum and the colon.

Table 5
GI location of compression-coated tablets 3 h after oral administration to fasted dogs

Formulation code	Location	
	Dog A	Dog B
TR-A	SI 5[a]	Colon
TR-B	SI 5[a]	Colon
TR-F	SI 5[a]	Colon

[a] The final fifth of the small intestine.

The mean AUC after oral administration of TR-A was 1.4 ± 0.5 μg h/ml and the mean C_{max} was 0.40 ± 0.25 μg/ml (Table 4). Since the AUC value of TR-A agreed with previous results (Sako et al., 1996a), it is thought that AAP was almost completely absorbed after oral administration. The results in Table 4 also clearly show that differences in the core tablet formulation can markedly influence bioavailability. After oral administration of TR-A, the AUC was 1.3-fold greater and the C_{max} 1.7-fold greater than the values for TR-B, and were 3.5- and 5.7-fold greater than those for TR-F. These results strongly suggest that the bioavailability of these formulations are not identical. Since AAP is absorbed equally well throughout the GI tract (Kimura et al., 1994), the marked difference in the AUC and C_{max} is thought to be caused by differences in the amount of drug released from each formulation.

Since the composition and amount of the outer layer of the formulations used in this study were the same, the gelation and dissolution of the outer layer is thought to have had no effect on the different in vivo bioavailability exhibited by these formulations. Therefore, to confirm the effect of core tablet erosion on pharmacokinetics, the statistical correlation between the core erosion ratio and AUC, and between the core erosion ratio and C_{max} were investigated. As shown in Figs. 4 and 5, both the AUC and the C_{max} of AAP in all dogs was greater for formulations with greater core erosion ratios. The Spearman's rank correlation coefficients were 0.71 ($P = 0.0097$) for the AUC and 0.68 ($P = 0.015$) for the C_{max}; both these values indicate the correlation is significant. These results indicate that compression-coated tablets with a greater core erosion ratio have higher AUC and C_{max} values than tablets with low core erosion ratios. Since the core erosion ratio of TR-F was only 24.6%, it is

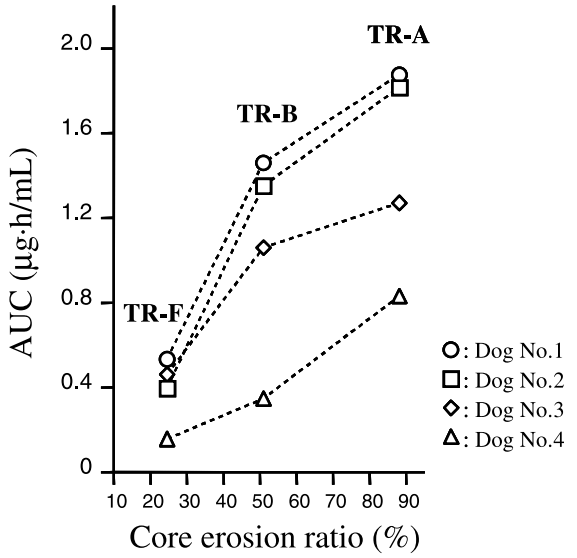

Fig. 4. Relationship between the core erosion ratio and the AUC of AAP after oral administration of compression-coated tablets to dogs. Each point represents the data for one dog.

possible that only one-fourth of the AAP in the formulation was released after the outer layer disintegrated. Additionally, because of the dearth of water in the ileum and colon, it is thought that AAP release from the uneroded core is markedly suppressed. The low AUC and C_{max} values for orally administered TR-F support this hypothesis. In contrast, the in vitro results indicate that more than 50% of the AAP in the TR-A and TR-B formulations could be released after their outer layer disintegrated; this is thought to have led to the larger amount of AAP in plasma from dogs given TR-A and TR-B compared to values in animals given TR-F. Additionally, both the AUC and C_{max} obtained in dog no. 4 were very low and were widely separated from values obtained in the other three dogs, even for the TR-A formulation. This observation might result from physiologic conditions specific to that animal, such as extremely low water content in the colon of or rapid GI transit in dog no. 4. These results indicate that compression-coated tablet cores that absorb water during their transit through the GI tract are able to release more drug in the lower GI tract where less water exists. Therefore, the core erosion ratio could prove to be an effective index to evaluate and model drug release from compression-coated tablet formulations designed to release their payloads in the lower GI tract.

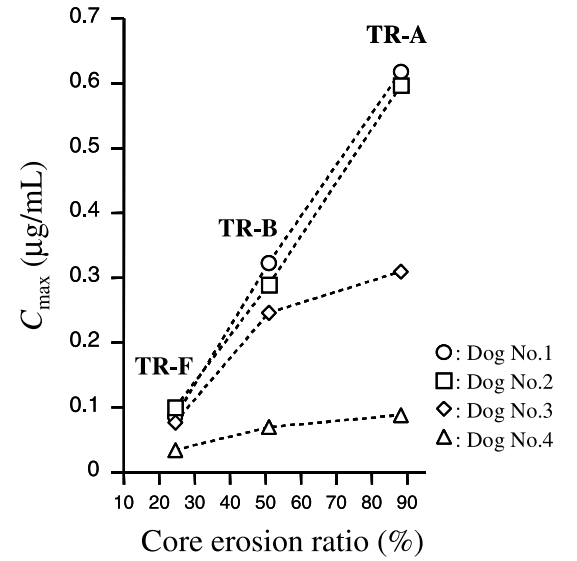

Fig. 5. Relationship between the core erosion ratio and the C_{max} of AAP after oral administration of compression-coated tablets to dogs. Each point represents the data for one dog.

4. Conclusion

In conclusion, the results of this study show that a new index, the core erosion ratio, of compression-coated tablets increases if highly water-soluble excipients are added to the core. Although formulations might possess similar in vitro AAP dissolution profiles, in vivo performance after oral administration of tablets with different core erosion ratio values can be markedly different. There is a positive correlation between a greater core erosion ratio and larger AUC and C_{max} values after oral administration to fasted dogs. This phenomenon can be explained by differences in drug release from the formulation in the lower GI tract. Therefore, the core erosion ratio should be taken into consideration when designing compression-coated timed-release formulations targeted for drug release in the lower GI tract.

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