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Comparison of the mechanical destructive force in the small intestine of dog and human

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Abstract

The purpose of this study was to evaluate the destructive force that oral solid dosage forms receive in the small intestine of dogs and humans. Information on the mechanical destructive forces of the gastrointestinal tract (GI) helps formulation design research in the following way: (1) to improve the predictability of the dissolution test since in vivo drug release is affected by not only agitation intensity but also mechanical stress; (2) to design safe and robust products by avoiding dose-dumping or unintended drug release at an inadequate site; (3) to better understand the species difference in bioavailability by comparing the destructive forces against dosage forms in the GI of dogs with those of humans. ''Destructive force Dependent Release System'' (DDRS) was developed to measure the mechanical destructive forces of the GI tract by using highly hydrophobic Teflon powder. In a DDRS, a marker drug contained in the core tablet is released only when the DDRS receives a force larger than its pre-determined crushing strength. DDRS-Small Intestine (DDRS-SI), a modified DDRS, was prepared for targeting the small intestine. DDRS-SI was encapsulated in starch capsules (Capill®) and then the capsules were coated with an enteric film (DDRS-SI-Ecap). The capsules were administered to six dogs and nine human volunteers. Both dogs and human volunteers crushed a DDRS-SI having a crushing strength of 1.2 N. Therefore, these controlled-release formulations should withstand a destructive force of 1.2 N when they pass through the small intestine. © 2002 Published by Elsevier Science B.V.

Keywords: Stomach; Small intestine; Destructive force; Teflon; Gastrointestinal transit

1. Introduction

The in vivo drug release profile of oral solid dosage forms cannot always be estimated by in vitro dissolution tests. Dissolution tests can simulate gastrointestinal (GI) conditions to some extent. However, the estimation of in vivo drug release from in vitro dissolution tests sometime ends in failure. One reason for the lack of in vivo–in vitro correlation is mechanical stress. Orally administered dosage forms receive stress by the peristaltic movement of the GI wall. In hy-

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drogel-type tablets, in vivo drug release was much faster than that expected from in vitro dissolution tests due to the peristalsis of the GI tract (Shameem et al., 1995).

Among the dissolution test conditions, hydrodynamic properties (agitation intensity) and mechanical destructive force are important factors which affect the dissolution behavior of the dosage form. Information on pH conditions in the GI tract and transit rates of the dosage forms through the GI tract has been analyzed to determine suitable dissolution test conditions (Dressman, 1986). Due to a lack of information on the mechanical destructive forces of the GI tract, current dissolution test methods are designed while giving little consideration to these forces. More specific information on the mechanical destructive forces of the GI tract will promote our understanding of the difference between the in vivo and in vitro response of oral dosage forms.

In the formulation design of the sustained release and colonic delivery dosage forms, we need to consider the effect of the mechanical destructive forces in the GI tract. These dosage forms are carried by peristaltic waves from the stomach to the lower part of the GI tract. It is obvious that the peristalsis in the stomach and small intestine applies some mechanical stress onto the tablets. These dosage forms should withstand this pressure until they reach the target site to avoid dose dumping or unintended drug release. To optimize the in vitro evaluation method for the mechanical robustness of dosage forms, the measurement of the destructive force in the stomach and small intestine is required.

As a part of the physiological process of food digestion, it was considered that the contents in the GI tract receive a maximum force by the peristaltic motion in the stomach, more precisely in the antrum. This means that the administered modified-release dosage forms should mainly resist the mechanical destructive forces of the stomach. However, the mechanical destructive forces of the small intestine are also important when we consider the physical properties of the dosage forms in wet conditions. Most of the solid oral dosage forms lose their mechanical strength by their immersion in water. After 4 h dissolution test, the mechanical strength of hydrogel-type tablets decreased from more than 20 to 0.5 N (Sako et al., 1996) and a similar decrease was observed in insoluble film-coated tablets (Hirasima et al., 1990). In general, the strength in the wet condition of the dosage form decreases as immersion time increases. Thus, a dosage form that successfully passes through the stomach without breaking can still be destroyed in the small intestine, which has a weaker peristalsis force, after having been in contact with the GI fluid for a few hours.

We already reported on a new device to evaluate the destructive force in the stomach (Kamba et al., 2000). We referred to this type of tablet as a 'Destructive force Dependent Release System' (DDRS). The mechanical destructive forces in the stomach of a human and dog were already evaluated as 1.9 and 3.2 N, respectively, using the DDRS (Kamba et al., 2000, 2001). In this study, a DDRS-Small Intestine (DDRS-SI) was prepared for targeting the small intestine by modifying the DDRS. DDRS-SI was encapsulated in starch capsules (Capill®) and then, the capsules were coated with an enteric film (DDRS-SI-Ecap). The destructive forces in the small intestine of dogs and humans were evaluated using this system.

2. Materials and methods

2.1. Materials

Teflon® powder (TE-820-J) was purchased from DuPont-Mitsui Fluorochemicals (Japan). AEA® (polyvinylacetal diethylaminoacetate) was obtained from Sankyo (Japan). Sulfisoxazole (SIX) and sulfamethizole (SMZ) were purchased from Sigma Chemical (USA). Acetaminophen (AAP, MW 151.2) and acetaminophen glucuronide (AAP-G, MW 349.3) were purchased from Sigma Chemical (USA). Polysorbate 80 was purchased from Kao (Japan). Hydroxypropylcellulose (HPC) and hydroxypropylmethylcellose phthalate HP-55 (HPMCP) were purchased from Shin-Etsu Chemical (Japan). Microcrystalline cellulose was purchased from Asahi Chemical (Japan). Starch

capsule (Capill®) was obtained from Capsugel (Japan). Pentagastrin was purchased from Sigma Chemical (USA). GA-test was obtained from the National Institute of Hygienic Sciences (Japan).

2.2. Structure and manufacturing process of DDRS-SI

The DDRS-SI contains the core tablet and an outer Teflon layer (200 mg of Teflon powder) as shown in Fig. 1. The diameter of the core tablet was 3 mm and that of the DDRS-SI was 7 mm. The core tablet consisted of 5 mg of a marker drug, 3.4 mg of lactose, 1.4 mg of microcrystalline cellulose, 0.1 mg of HPC and 0.1 mg of magnesium stearate. The core tablets A, B and C contained SIX, SMZ and acetaminophen, respectively. The DDRS-SI was prepared by a powder compressing device (Rheometer, NRM-2010J-CW, Fudohkogyo, Japan) with two flat-face punches and a die. The crushing strength of the DDRS-SI was regulated by changing the compression force.

The DDRS-SI was encapsulated in Capill® and then the capsule was enteric-coated with HPMCP HP-55 using a coating machine (DRC-200, Powrex, Japan) under standard operating conditions. HPMCP HP-55 only dissolves in environments of pH above 5.5 and does not dissolve in acidic environments. The capsule was named DDRS-SI-Ecap.

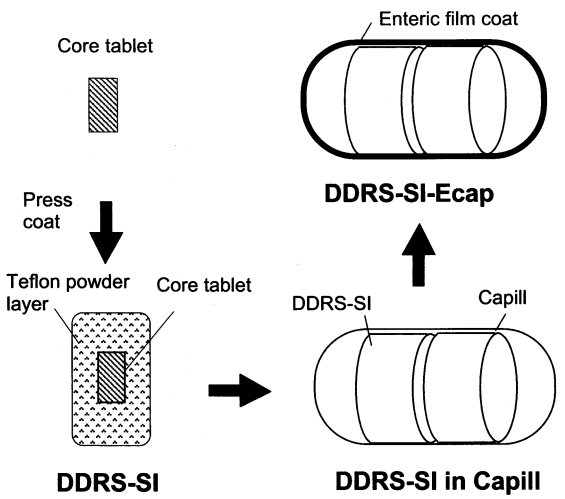

Fig. 1. Cross section of Teflon® tablet (DDRS-SI) and scheme of the DDRS-SI-Ecap.

2.3. Measurement of the crushing strength of DDRS-SI

The crushing strength of the DDRS-SI was determined using a Rheometer (Fudohkogyo, NRM-2010J-CW, Japan). The test was carried out in Japanese Pharmacopoeia (JP) XII second fluid (pH 6.8) at 37 °C. The DDRS-SI was pressed against the adapter in the direction of the diameter in a manner similar to that measuring the hardness of tablets with a general tablet-hardness tester.

2.4. Physical characteristics of core tablets, DDRS-SI and DDRS-SI-Ecap

Disintegration tests of the core tablet A, B and C were carried out in JP XII first fluid (pH 1.2), and second fluid (pH 6.8) using JP XII disintegration test apparatus with disks. Disintegration tests of DDRS-SI were carried out for 6 h in JP first fluid and second fluid. Soaking tests of DDRS-SI was carried out for 6 h at 37 °C in 100 ml of JP second fluid with surfactant (0.35 w/v% Polysorbate 80), then the crushing strength of DDRS-SI was measured. Disintegration tests of the DDRS-SI-Ecap were carried out in JP first fluid for 2 h, and then the test fluid was changed to JP second fluid. This method was the same as that for JP enteric-coated formulations. However, the residual of the DDRS-SIs encapsulated in the DDRS-SI-Ecap was ignored. In a separate set of experiments, the DDRS-SI-Ecap received a mechanical force of 4.9 N by the Rheometer after the disintegration test in JP first fluid for 2 h. The resulting appearance of the capsules and internal DDRS-SI was visually examined.

2.5. In vivo dog study

Nine dogs (male beagle, weight 11.0–13.0 kg) were used in this study. Three of the nine dogs were used as controls. The enteric-coated starch capsules containing the core tablets A and B were

administered to the dogs. Then the plasma concentration profiles of the marker drugs were obtained. The DDRS-SI-Ecaps were administered to six dogs twice with a 1-week washout period. In the first experiment, DDRS-SI-Ecaps containing DDRS-SIs having a crushing strength of 0.8 and 1.7 N were administered. The former included the core tablet A and the latter included the core tablet B. In the second experiment, DDRS-SI-Ecaps containing the DDRS-SIs having a crushing strength of 0.9 and 1.2 N were administered. The former included the core tablet A and the latter included core tablet B. Prior to each experiment, the dogs were fasted for 18 h with free access to water. During the experiment, the dogs were allowed to take water freely. Blood samples were collected from each dog at 0, 1, 2, 4, and 6 h after administration. The samples were stored at − 80 °C until assay. In order to control the pH of gastric fluid, 12 μg/kg of pentagastrin was injected to the muscle at 0.5 h prior to administration, and at 0, 0.5, 1 and 1.5 h after administration.

2.6. Assay for marker drugs in dog plasma

The marker drugs, SIX and SMZ, in plasma were determined by HPLC. The plasma sample was diluted with 0.03 w/v% CH_3COONH_4 buffer, and 6% trichloroacetic acid in methanol was added. The mixture was shaken for 30 s and centrifuged at 3000 rpm for 10 min. The supernatant was taken and injected into the HPLC system. Conditions for the HPLC system were as follows: column, YMC-Pack ODS-AM AM-312, 6.0 mm × 15 cm (YMC, Japan); mobile phase, 0.03% CH_3COONH_4 buffer–methanol (98:2, v/v); flow rate, 2.0 ml/min; detector, UV-spectrophotometer SPD-10A (Shimadzu, Japan); wave length, 260 nm. The calibration curves of SIX and SMZ in the concentration of 0–25 μg/ml were $Y = 0.000214X - 0.0588$ ($r = 0.9999$) and $Y = 0.000198X - 0.0202$ ($r = 0.9999$), respectively. The coefficient variations (CV) of SIX and SMZ at the concentration of 1 μg/ml in the calibration curves were 3.75% ($n = 6$) and 5.65% ($n = 6$), respectively. The recoveries of SIX and SMZ in the concentration of 1 μg/ml were 92.1 and 101.2%, respectively.

2.7. In vivo human study

Nine healthy male subjects (age 25–55 years old, weight 50–70 kg) participated in this study with written informed consent. The candidates had been screened in advance with the GA-test (Ogata et al., 1984) and those who showed gastric subacidity were excluded from this study. Before the study of DDRS-SI-Ecaps, the subjects were administered with the core tablet C (acetaminophen) encapsulated in enteric-coated Capill® after having fasted overnight. The excretion rates and extents of acetaminophen glucuronide in the urine were determined.

In the DDRS-SI-Ecap studies, all subjects were fasted overnight before administration. The DDRS-SI-Ecap was administered with 100 ml of water. During the studies, subjects were allowed to take water freely. Urine samples were collected from each subject at 0, 2, 4, 6, and 8 h after administration and the volume of urine was measured. The samples were stored at − 80 °C until assay.

DDRS-SIs with crushing strengths of 0.6, 0.7, 0.8, 0.9, 1.2, 1.7 and 1.8 N were prepared. Initially DDRS-SI-Ecaps containing DDRS-SI with a crushing strength of 0.8 N (CS-0.8 N) were administered to all subjects. After a washout period of 3 or 4 days, subjects who had crushed the DDRS-SI CS-0.8 N in the first study were administered with the DDRS-SI-Ecaps containing a DDRS-SI of the next higher crushing strength. Those who had not crushed the DDRS-SI CS-0.8 N were administered with the DDRS-SI-Ecaps containing a DDRS-SI of the next lower crushing strength. In this way, subjects were sequentially administered with three or four DDRS-SI-Ecaps every 3 or 4 days.

2.8. Assay for marker drug in human urine

About 50% of the administered AAP is excreted in the urine as a glucuronide and the excretion percentage of unchanged AAP is very small (Bales et al., 1984). In our study, the AAP-G in the urine was assayed by the HPLC method. Conditions for the HPLC system were as follows: column, TSK-GEL ODS-80Ts, 4.6 mm × 15 cm (Tosoh, Japan);

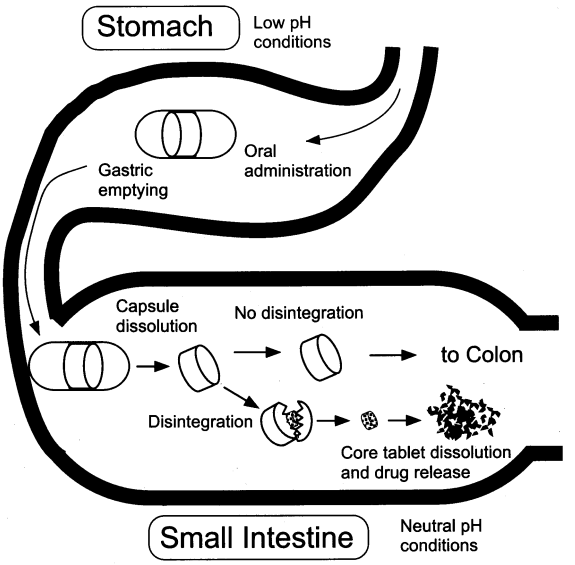

Fig. 2. Schematic diagram of DDRS-SI mechanism of action in the GI tract.

mobile phase, 0.02 mol/l H_3PO_4–acetonitrile (97.5:2.5, v/v); flow rate, 1.0 ml/min; detector, UV-spectrophotometer SPD-10A (Shimadzu, Japan); wave length, 250 nm. The urine sample was centrifuged at 3000 rpm for 5 min and 50 ml of the supernatant was subjected to HPLC analysis. The calibration curve in the concentration of 0–100 μg/ml was $Y = 0.000108X - 0.8599$ ($r = 0.9999$). The coefficient variation (CV) in the concentration of 10 μg/ml in the calibration curve was 4.18% ($n = 6$). The recovery in the concentration of 10 μg/ml was 87.0%.

2.9. DDRS-SI-Ecap mechanism of action

The action mechanism of DDRS-SI-Ecap is as follows (Fig. 2). After orally administration of DDRS-SI-Ecap, the DDRS-SI-Ecap goes through the stomach keeping its form intact owing to the rigid starch capsule coated with an enteric film. Then the enteric film and the capsule shell of DDRS-SI-Ecap dissolve in the upper small intestine and release the DDRS-SIs. The DDRS-SIs receive contraction forces from the small intestine wall. When the destructive force is larger than the crushing strength of the DDRS-SI, the outer Teflon layer breaks, the core tablet is exposed to the small intestinal fluid, and then the core tablet disintegrates immediately. The marker drug is then released and absorbed. The crushing of the DDRS-SI can be detected by the appearance of the marker drug in the plasma and/or urine. When the destructive force in the small intestine is smaller than the crushing strength of the DDRS-SI, the DDRS-SI retains its shape and is carried toward the colon.

DDRS-SI was designed in consideration of the following physiological conditions. The gastric fluid pH in dogs that received a pentagastrin treatment is 1.0–2.0 (Yamada et al., 1990). The intestinal fluid pH in untreated dogs is 6.0 (Lui et al., 1986). The gastric emptying of a large-size dosage form in dogs under fasting conditions that received a pentagastrin (PG) treatment is over 1.5 h. The gastric emptying of a large-size dosage form (9 mm in diameter) did not occur when gastrin was administered at regular intervals for a period of 1.5 h (Fukui et al., 2000). The small intestinal transit time of a large-size dosage form in dogs is 2–3 h (Davis et al., 1993; Fukui et al., 2000). The pH of the gastric fluid in human subjects without gastric subacidity is 1.1 and that of the intestinal fluid is 6.0 (Lui et al., 1986). The gastric emptying rate of a large-size dosage form in human is less than 2 h under fasting conditions (Kenyon et al., 1994). In their study, a capsule of 22 mm in length was used. The small intestinal transit time of a large-size dosage form in human is 3–4 h (Davis et al., 1986).

3. Results

3.1. Physical properties of the DDRS-SI

The core tablets A, B and C were disintegrated in less than 1 min under acidic (pH 1.2) and neutral (pH 6.8) conditions. The relationship between the compression force and the crushing strength of the DDRS-SI is shown in Fig. 3. The crushing strengths of DDRS-SIs were prepared as 0.6, 0.7, 0.8, 0.9, 1.2, 1.7 and 1.8 N. In the soaking test, the soaking in JP second fluid with surfactant for 6 h did not affect the crushing

strength of the DDRS-SIs. In the disintegration test, the DDRS-SIs were not disintegrated under acidic and neutral conditions for over 6 h even in the most fragile DDRS-SI (0.6 N). After the disintegration test, the outer Teflon® layer and the core tablet of the DDRS-SI looked intact. This shows that the accumulation of weak destructive forces does not cause a crushing of the DDRS-SI.

The DDRS-SI-Ecap was not disintegrated for 2 h at pH 1.2, but was disintegrated within 9 min at pH 6.8. These results matched the JP XII requirement for enteric dosage forms. The DDRS-SI-Ecap was undamaged after 2 h in a disintegration test at pH 1.2 followed by application of a mechanical strain of 4.9 N and the inner DDRS-SIs were kept unchanged during the process. The destructive forces in the stomach of human and dog were previously evaluated to be 1.9 and 3.2 N, respectively (Kamba et al., 2000, 2001). The mechanical strain of 4.9 N (500 gf) was considered to be large enough after comparing it to the destructive force in the stomachs of human or dog. Consequently, the DDRS-SI-Ecap was hard enough to reach the duodenum of human and dog without breaking.

3.2. In vivo dog study

The drug concentrations in the plasma of the control dogs after administration of the enteric-coated starch capsule containing the core tablets A and B are shown in Fig. 4. The marker drugs were detected in plasma 4 h after the administration.

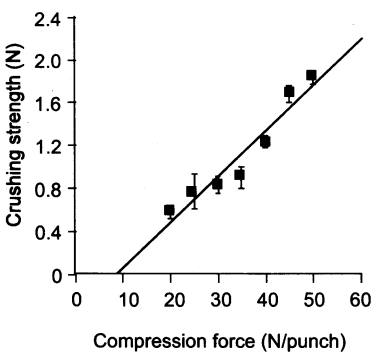

Fig. 3. Relationship between compression force and crushing strength of DDRS-SI. ■: Mean of three measurements with S.D. bars.

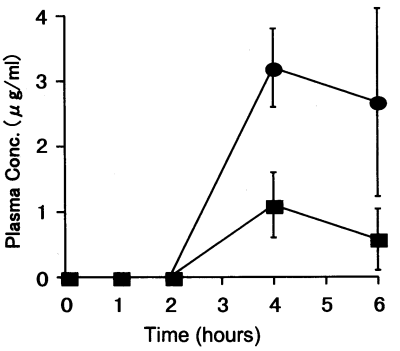

Fig. 4. Plasma concentration of SIX and SMZ after administration of core tablet A and B encapsulated in enteric-coated Capill® in pentagastrin pre-treated dog. Each plot shows the mean ± S.D. ($n = 3$). Symbols: (●) Core tablet A [SIX] (encapsulated in enteric-coated Capill®), (■) Core tablet B [SMX] (encapsulated in enteric-coated Capill®).

DDRS-SIs with crushing strengths of 0.8, 0.9, 1.2 and 1.7 N (CS-0.8 N, CS-0.9 N, CS-1.2 N, CS-1.7 N) were administered to six beagle dogs. The profiles of drug concentrations in the plasma for each dog are shown in Fig. 5. In the case of dog D113, the marker drugs released from DDRS-SI CS-0.8 N and CS-0.9 N were detected in the plasma. On the other hand, the marker drug, SMZ, included in DDRS-SI CS-1.2 N and CS-1.7 N was not detected in the plasma. Therefore, DDRS-SI CS-0.8 N and CS-0.9 N were considered to be destroyed in the small intestine, but CS-1.2 N and CS-1.7 were not. This means that the destructive force in dog D113 can be evaluated as 0.9 N. The data from the other five dogs were interpreted the same as those from D113.

Unfortunately, the DDRS-SI-Ecap, which contained DDRS-SI CS-0.9 N and CS-1.2 N, did not dissolve in the GI tract when administered to dog D115, for the intact capsule was found in the feces. Therefore, this experiment did not give any information on the destructive force of the small intestine. The other five dogs crushed the DDRS-SI CS-0.9 N and only one dog (D114) crushed the DDRS-SI CS-1.2 N (Fig. 6). Dog D13 did not crush the DDRS-SI CS-0.8 N, but did crush the DDRS-SI CS-0.9 N. These results showed that

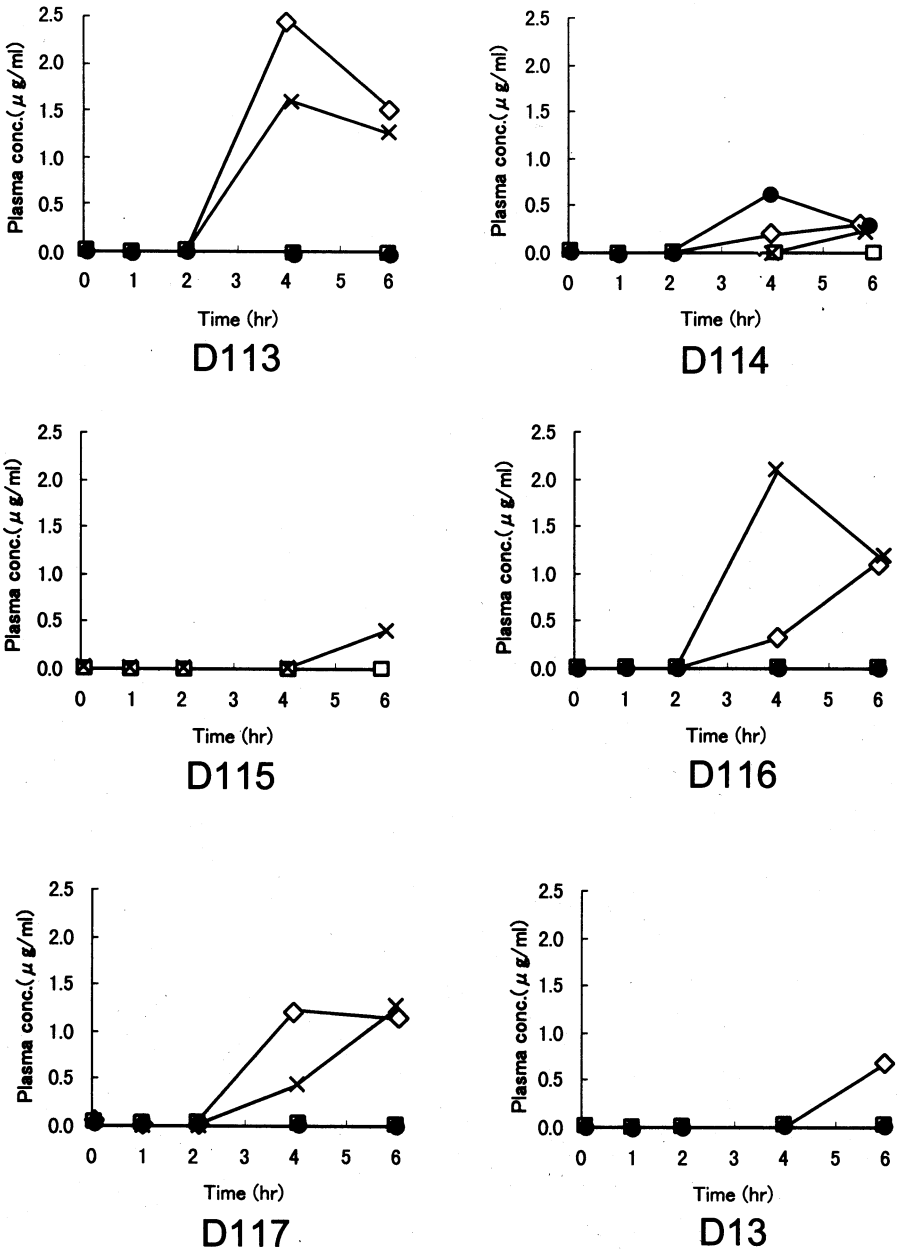

Fig. 5. Plasma concentration of SIX and SMZ after administration of DDRS-SI-Ecaps in dogs. Symbols: (×) DDRS-SI CS-0.8 N [SIX], (◇) DDRS-SI CS-0.9 N [SIX], (●) DDRS-SI CS-1.2 N [SMZ], (□) DDRS-SI CS-1.7 N [SMZ]. D115 (Dog No. 115) has no data regarding DDRS-SI CS-0.9 N and CS-1.2 N.

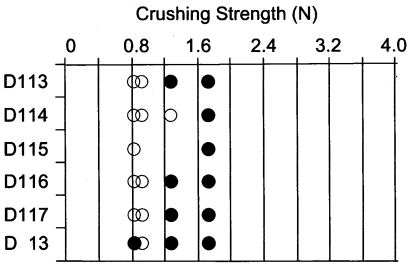

Fig. 6. Destructive force in dog small intestine. Symbols: (○) crushed, (●) not crushed. D115 (Dog No. 115) has no data regarding DDRS-SI CS-0.9 N and CS-1.2 N.

the small intestine of the dog can potentially crush tablets that have a crushing strength of 1.2 N.

3.3. In vivo human study

Fig. 7 shows the urinary excretion of acetaminophen glucuronide after administration of the control capsule and DDRS-SI-Ecaps to nine subjects. The control capsule was an enteric-coated capsule filled with the core tablet C. Tablet C contained acetaminophen as a marker drug. In the case of subject 1, acetaminophen glucuronide (AAP-G) was excreted in the urine 4–6 h after administration of the control capsule. AAP-G was detected after the administration of the DDRS-SI CS-0.8 N and CS-1.2 N, but not after the administration of DDRS-SI CS-1.7 N. This means that the destructive force in the small intestine of subject 1 was between 1.2 and 1.7 N. The other eight subjects were also administered with DDRS-SI-Ecaps three or four times, and the range of destructive force in the small intestine was evaluated.

The results of the nine subjects are summarized in Fig. 8. Five of the eight subjects crushed the DDRS-SI CS-1.2 N and no subject crushed the DDRS-SI CS-1.7 N. These results showed that the small intestine of the human can potentially crush tablet that have a crushing strength of 1.2 N.

4. Discussion

Two marker drugs were used for the dog study. The pharmacokinetic properties of the marker drugs had already been studied (Yoshitomi et al., 1993; Slywka et al., 1976). Further, those marker drugs were successfully used in our dog stomach study. To obtain the reference plasma concentration profiles of the marker drugs when they are released from enteric dosage forms in a dog GI tract, enteric-coated capsules (Capill®) filled with marker drugs in each core tablet were administered to three dogs (Fig. 4). The plasma concentration of the marker drugs was high enough to detect the release of the marker drugs in the small intestine. The time of appearance of the marker drug in plasma is considered to be an index for the gastric emptying time of the administered enteric capsules. From the plasma concentration profiles in Fig. 4, the gastric emptying time in this study was estimated to be 2 h; more precisely, it was somewhere between 2 and 4 h. Taking the dissolution time of the enteric capsules into account, the gastric emptying time was slightly longer than that reported (Mojaverian et al., 1987; Aoyagi et al., 1992). Pentagastrin may provide a plausible explanation for this delay. Pentagastrin was used to lower the gastric pH in this study. However, it is reported that a treatment with pentagastrin can extend the gastric emptying time of dogs (Dozois and Kelly, 1971; Fukui et al., 2000).

The initial appearance of the marker drugs in plasma is considered to represent the time of the marker drug released from the DDRS-SI. Consequently, it is possible to estimate the crush site of DDRS-SI in the GI tract based on information about gastric transition of dosage forms. It was observed that controlled-release tablets reached the colon in 2–3 h after dosing in dogs (Sako et al., 1996). However, most studies concluded that the colon arrival time of controlled-release tablets was 3–4 h and the average small intestine transit time was 2–3 h in dogs (Davis et al., 1993; Takaya et al., 1995; Fukui et al., 2000; Jeong et al., 2001). In this study, the gastric emptying time of enteric-coated Capill® was 2–4 h. Based on this knowledge, the colon arrival time of DDRS-SI in this study was estimated to be longer than 4 h post-dose. Consequently, an onset time of plasma marker drugs within 4 h means that the DDRS-SI was crushed in the small intestine. Alternatively, an onset time of over 4 h means that there is a possibility that the tablet was crushed in the large

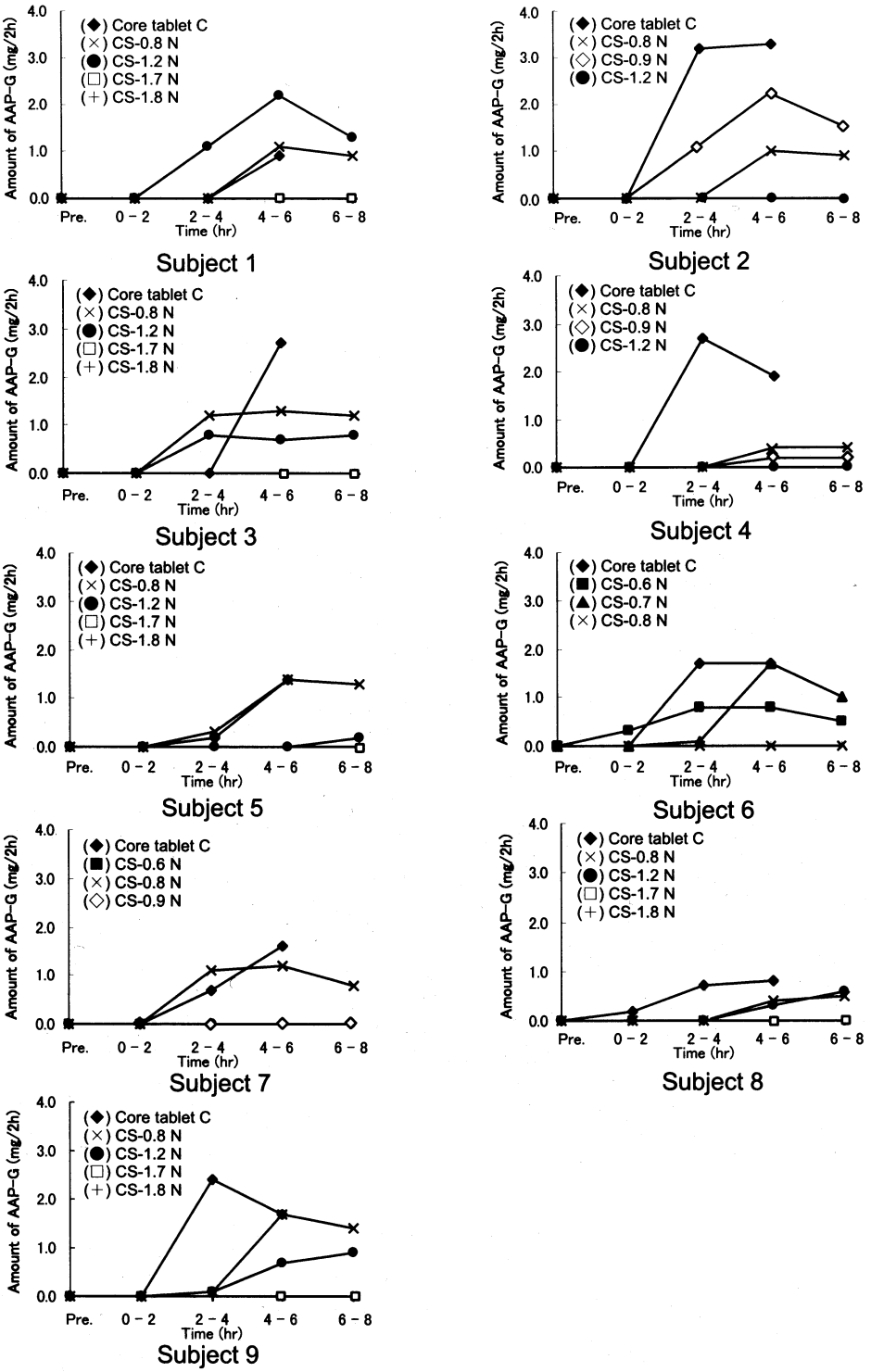

Fig. 7. Urinary excretion of acetaminophen glucuronide after administration of DDRS-SI-Ecaps and a core tablet in subjects. Symbols: (◆) Core tablet C encapsulated in enteric-coated Capill®, (■) DDRS-SI CS-0.6 N, (▲) DDRS-SI CS-0.7 N, (×) DDRS-SI CS-0.8 N, (◇) DDRS-SI CS-0.9 N, (●) DDRS-SI CS-1.2 N, (□) DDRS-SI CS-1.7 N, (+) DDRS-SI CS-1.8 N.

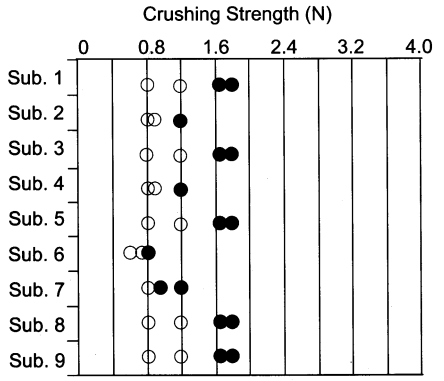

Fig. 8. Destructive force in human small intestine. Symbols: (○) crushed, (●) not crushed.

intestine. There were three cases of a tablet being crushed at over 4 h after onset, CS-0.8 N in D114, CS-0.8 N in D115 and CS-0.8 N in D13. In the case of CS-0.8 N in D114, the same dog crushed CS-0.9 N and CS-1.2 N with an onset time of 2 h. Consequently, it was concluded that the small intestine of this dog (D114) had a maximum destructive force of 1.2 N, regardless of the crush site of CS-0.8 N. In the other two cases, we cannot neglect the possibility of the tablet being crushed in the large intestine. However, even in D115 and D13, there was no crushing of CS-1.7 N during the small intestine transit.

The conclusion of the dog DDRS-SI study is that the maximum destructive force of the small intestine in dogs is 1.2 N. In other words, the destructive force in the small intestine of dogs is not so strong as it could destroy the dosage form with a mechanical strength of 1.7 N or more.

AAP was used as a marker drug in the human study. Prior to DDRS-SI administration, the urinary excretion of the marker drug from the core tablets released in the small intestine was studied (Fig. 7). The onset times of AAP-G urinary excretion in control capsules were 0–2 h for one subject, 2–4 h for eight subjects and 4–6 h for one subject. The onset time of urinary excretion is considered to be the sum of the gastric emptying time, dissolution time for enteric-coated Capill® and core tablets and the time for absorption, distribution, metabolism and excretion of AAP. Meanwhile, the small intestine transit time is 3–4 h in human (Davis et al., 1986). Consequently, a DDRS-SI with an onset time shorter than 6 h was most probably crushed in the small intestine. There was only one case with an onset time of over 6 h, CS-1.2 N in subject No. 5. This subject may have crushed the tablet in the large intestine. Setting aside the data of subject No. 5, due to the uncertainty of the crush site, it could still be concluded that the maximum destructive force of the human small intestine is 1.2 N.

The mechanical destructive forces in the small intestine of dogs and humans were in a similar range (0.8–1.2 N). In our previous studies, the obtained mechanical destructive force in the stomach of humans was 1.9 N (Kamba et al., 2000) and that of dogs was 3.2 N (Kamba et al., 2001). This means that dogs have a stronger stomach destructive force than humans. On the other hand, the destructive forces of the small intestine in both species are within the same range. It is worth noting that the orally administered dosage forms receive strongest mechanical stress in the stomach during their transit through the GI tract to the distal small intestine in both humans and dogs.

The crushing strength (hardness) of sustained-release tablets is roughly over 19 N before their administration (Sako et al., 1996). Therefore, the tablets should not be crushed by the contractile force of the GI tract. The crushing strength of the tablets, however, decreases with soaking in GI fluid. According to the previous study of Sako et al. (1996), in a hydrogel matrix formulation, the mechanical strength decreased to less than 0.5 N after soaking for 4 h in water. A hydrophilic gel layer is more likely to be eroded at a faster rate than the formulation researcher expected and the whole tablet may be crushed at an unintended site due to the GI motility.

It is thus possible that hydrophilic matrix tablets, wax matrix tablet, enteric-coated tablet, enteric-coated capsule, and colon-targeted devices, will release their drug at unintended sites. In developing these controlled-release formulations, the crushing strength after administration needs to be carefully examined to ensure reproducible bioavailabilities.

5. Conclusions

Our study showed that the small intestine of dogs and humans potentially have a mechanical destructive force of 1.2 N. This value can be used as an evaluation criteria for dose dumping in developing controlled-release dosage forms. The information will help us to understand the reason for the differences between in vitro and in vivo dissolution properties of dosage forms.

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