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A unique dosage form to evaluate the mechanical destructive force in the gastrointestinal tract

Masaharu Kamba [a,*], Yasuo Seta [a], Akira Kusai [a], Masaru Ikeda [a], Kenji Nishimura [b]

[a] *Product Development Laboratories, Sankyo Co., Ltd, 2-58, 1-chome, Hiromachi, Shinagawa-ku, Tokyo 140, Japan*
[b] *Drug Metabolism and Pharmacokinetics Research Laboratories, Sankyo Co. Ltd, 2-58, 1-chome, Hiromachi, Shinagawa-ku, Tokyo 140, Japan*

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Abstract

The purpose of this study was to prepare tablets that could evaluate the destructive force in the gastrointestinal (GI) tract. Many factors are known to affect in vivo drug release from oral dosage forms. There is still relatively little information on the mechanical destructive force in the GI tract. Press-coated tablets with an extremely brittle outer layer were developed using a unique, highly hydrophobic Teflon powder that could be shaped with weak compression force. A marker drug contained in the tablets was released only when the tablets received a force larger than its predetermined crushing strength. We referred to this type of tablet as a 'destructive force dependent release system' (DDRS). A total of nine healthy, male subjects were orally administered the tablets under fed and/or fasting conditions. Tablets with a predetermined crushing strength of 1.50 N were crushed by all of the four subjects who took them under fed conditions and two of the five subjects under fasting conditions. Tablets with a crushing strength of 1.89 N were crushed by two of the six subjects who took them under fed conditions and none of the five subjects under fasting conditions. The range of mechanical destructive force in the human stomach was obtained.

Keywords: Stomach; Destructive force; Teflon; Gastrointestinal transit; Riboflavin

1. Introduction

In order to establish a rational dissolution test that can predict in vivo drug release, we need to understand the physiological conditions in the gastrointestinal (GI) tract. Although much data has been collected on pH conditions (Lui et al., 1986; Chan et al., 1990; Mojaverian et al., 1991) and transit rates of dosage forms in the GI tract (Meyer et al., 1979; Davis et al., 1986, 1988; Kenyon et al., 1994), we still have relatively limited information on the mechanical

* Corresponding author. Tel.: +81-3-34923131; fax: +81-3-54368568.
E-mail address: kmash@shina.sankyo.co.jp (M. Kamba).

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destructive force there. This information is necessary to design oral dosage forms, especially sustained-release and colonic delivery formulations (Steffensen and Pedersen, 1986). Dose dumping, or the crushing of dosage forms at an unexpected site in the GI tract, impairs the reliability of the formulation's effectiveness.

A manometer (Stanghellini and Malagelada, 1983) and pressure-sensitive radio telemetry capsules (Coupe et al., 1991) have been used to monitor the GI contraction waves, but the sizes and forms of the sensors used in these studies were much larger than those of actually marketed tablets or capsules. Thus, in those studies, it was difficult to estimate the mechanical destructive force applied to the dosage forms within the GI tract. Several recent studies have investigated the effect of the mechanical destructive force in the GI tract on in vivo drug dissolution (Katori et al., 1995; Shameem et al., 1995). However, the tablets used in these studies were made from hydrophilic materials. So the crushing strength of the dosage forms decreased with an increase in soaking time in the GI fluid, making it impossible to determine the exact destructive force applied when the dosage forms were crushed in the GI tract. When tablets are used as a standard to measure the destructive force in the GI tracts, the tablets must meet the following requirements: (1) the crushing strength of the tablets can be well controlled; (2) soaking in GI fluid does not affect the crushing strength; (3) the crushing in the GI tract can easily be detected; and (4) the shape and size of the tablets are similar to ordinary tablets.

This study presents a new method to evaluate the destructive force in the GI tract using a unique material, Teflon powder with ideal characteristics. It is very hydrophobic and it does not dissolve in any media. Further, it can be easily shaped into brittle mass with only a small compression force. Based on these characteristics, it was possible to design a dosage form which releases a marker drug only when the tablet received a force larger than its predetermined crushing strength.

2. Materials and methods

2.1. Materials

Teflon® powder (TE-820-J, TE-914-J) was purchased from DuPont-Mitsui Fluorochemicals (Japan). AEA® (polyvinylacetal diethylaminoacetate) was obtained from Sankyo (Japan). Riboflavin was purchased from Tokyo Tanabe (Japan). Carboxymethylcellulose was purchased from Gotoku (Japan). Magnesium stearate was purchased from Nippon Oil and Fat (Japan). Polysorbate 80 was purchased from Kao (Japan). Gelatin capsules (size #00) were purchased from Matsuya (Japan).

2.2. Hydrophobicity of compressed Teflon powder

The apparent contact angle between the surface of the compressed Teflon powder and water was measured by a sessile drop method using a Contact-Angle Meter (FACE, Kyowa Kaimenkagaku, Japan). A fraction of Teflon powder of particle size 355–500 μm was collected and compressed by a powder compressing device (Powder Press, Shimadzu, Japan) with a die and two flat-face punches (diameter 7 mm, 98 N/punch). A droplet of purified water (diameter 2 mm) was placed on the powder surface.

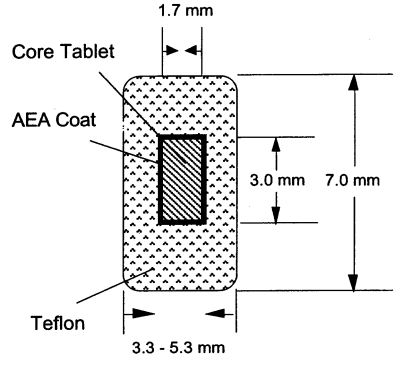

Fig. 1. Cross section of Teflon tablet (DDRS).

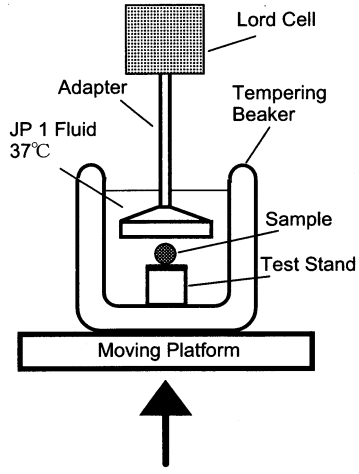

Fig. 2. Schematic diagram of rheometer.

2.3. Structure of the destructive force dependent release system (DDRS) and process of its manufacture

The DDRS was a press-coated tablet consisting of a core tablet and an outer Teflon layer (200 mg of Teflon powder) (Fig. 1). The core tablet (5 mg of riboflavin, 4.9 mg of carboxymethylcellulose and 0.1 mg of magnesium stearate) was coated with an AEA film (1 mg) by dipping it into the AEA solution, 6 w/w% in ethanol-acetone (1:1) mixture. The AEA dissolves only in acidic environments and it does not dissolve in environments of pH over 4. The AEA filmcoat thus prevents drug release from the core tablet under neutral or alkaline environments. The powder compressing device (Powder Press, Shimadzu, Japan) with two flat-face punches and a die was used to prepare the DDRS. The crushing strength of the DDRS was regulated by changing the compression force and grade of Teflon powder. The DDRS was encapsulated in a gelatin capsule. Riboflavin was selected as the marker drug because there have been many pharmaceutical studies using riboflavin (Ogata et al., 1984) and it does not readily exert a pharmacological action following oral administration.

2.4. Measurement of crushing strength

The crushing strength of the DDRSs was determined using a rheometer (Fudohkogyo, NRM-2010J-CW, Japan) (Fig. 2). The tests were carried out at 37°C in Japanese Pharmacopoeia (JP) XII first fluid (pH 1.2). While a moving platform was elevated at a constant rate (2 mm/min), the DDRS was pressed against the adapter in the direction of the diameter using the same manner applied when measuring the hardness of tablets by general tablet hardness testers.

2.5. Dissolution test, disintegration test and soaking test

Dissolution tests of the tablets by the paddle method (50 rpm, JP XII apparatus 2) were carried out for 6 h at 37°C in 900 ml of JP XII first fluid (pH 1.2) and second fluid (pH 6.8) with surfactant (0.35 w/v% polysorbate 80). The concentration of polysorbate 80 was considerably higher than its critical micelle concentration in water (Wan and Lee, 1974). The amount of riboflavin dissolved in the test fluid was determined spectrophotometrically. Disintegration tests of the tablets were carried out for 6 h at 37°C in JP XII first fluid using a JP XII disintegration apparatus with disks. Soaking tests of the tablets were carried out for 6 h at 37°C in 100 ml of JP XII first fluid and second fluid with surfactant (0.35 w/v% polysorbate 80). The crushing strength of DDRS was measured after soaking.

2.6. In vivo study

A total of nine healthy male subjects (age 28–46 years old, weight 50–71 kg) participated in this study with written informed consent. In the study with DDRS, candidate subjects had been screened in advance by administration of the core tablet coated with AEA after having fasted overnight. Based on measurements of the excretion rate and extent of riboflavin in the urine of these subjects, those who showed gastric subacidity were excluded from this study. The criteria of gastric subacidity was that the excretion of riboflavin after administration of core tablet coated with AEA was less than 150 μg in 2 h (Ogata et al., 1984). This is because the DDRS system does not work in subjects with gastric subacidity. Before administration, all subjects were fasted overnight. In the fed

condition, an encapsulated DDRS was administered with 100 ml of water at 30 min after a low-riboflavin breakfast. The breakfast consisted of 220 g of cooked rice and 350 ml of barley tea (extract of roasted barleycorn). During the studies under both fed and fasting conditions, subjects were allowed to take water ad libitum. The studies under fasting conditions were carried out using the same methods used under fed conditions except that the subjects did not take any food. Urine samples were collected from each subject at 1, 2, 4, and 6 h after administration and the volume of urine was measured. The samples were stored at −80°C until assay. The control samples were collected just before the administration of DDRSs to determine the basal excretion level of riboflavin for each subject. DDRSs with crushing strengths of 1.50, 1.89 and 3.04 N were prepared. Initially a DDRS with a crushing strength of 1.89 N (CS-1.89 N) was administered to subjects under both fed and fasting conditions. After a washout period of 3 or 4 days, the subjects who had crushed the DDRS with CS-1.89 N in the first study were administered DDRS with CS-3.04 N, and those who had not crushed the DDRS with CS-1.89 N were administered DDRS with CS-1.50 N.

2.7. Assay for riboflavin in urine

The riboflavin was assayed by a modified method described by Ogata et al. (1984). The concentration of riboflavin in the urine was determined by the HPLC method. Conditions for the HPLC system were as follows: column, TSK-GEL ODS-80Ts (4.6 mm × 15 cm) (Tosoh, Japan); mobile phase, 0.01 mol/l KH_2PO_4-methanol (65:35 in volume; pH 5 adjusted by 1 mol/l NaOH); flow rate, 1.0 ml/min; detector, fluorescence spectrophotometer F-1050 (Hitachi, Japan) (Ex 360 nm, Em 530 nm). The urine sample was centrifuged at 3000 rpm for 5 min and 50 μl of supernatant was subjected to HPLC analysis.

2.8. Strategy for the DDRS

Fig. 3 illustrates the schematic diagram of the DDRS behavior in the stomach. Encapsulated DDRS is administered orally. The hard gelatin capsule protects the DDRS from destruction during handling before administration and during its passage through the mouth and the esophagus, and then it dissolves in the stomach to release DDRS. The DDRS receives a contraction force from the stomach wall and the stomach contents. When the destructive force is larger than the crushing strength of the DDRS, the outer layer breaks, and the core tablet is then exposed to the gastric juice to immediately disintegrate. The marker drug is then released, absorbed, and excreted in the urine. The destruction of the DDRS can be detected by the increase of marker drug (riboflavin) excretion in the urine. When the destructive force in the stomach is smaller than the crushing strength of the DDRS, the DDRS keeps its shape and is carried toward the small intestine and colon. Even if the DDRS is crushed in the small intestine or colon, the core tablet coated with AEA does not disintegrate in the intestinal fluid.

The DDRS was designed based on the following physiological conditions. The pH of the gastric juice in human subjects without gastric subacidity is 1.1 and that of the intestinal juice is 6.0 (Lui et al., 1986). The gastric emptying rates of large-size dosage forms are less than 2 h under fasting conditions and from 2 to 12 h under fed conditions in humans (Kenyon et al., 1994).

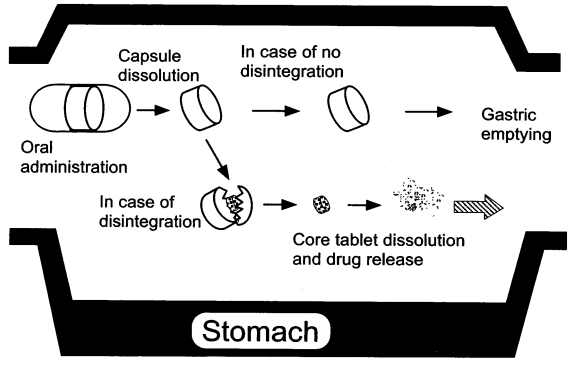

Fig. 3. Schematic diagram of DDRS behavior in stomach.

Table 1
Physical properties of Teflon® particle

Grade	Particle size (μm)[a]	Contact angle (°)[b]
TE-820-J	355–500	123
TE-914-J	355–500	136

[a] The fraction used in this study.
[b] Apparent contact angle to water.

3. Results

3.1. Hydrophobicity of compressed Teflon powder

The apparent contact angle between the surface of the compressed Teflon powder bed and water was much larger than 90° in both Teflon grades (Table 1). The hydrophobicity of Teflon is so great that a water droplet placed on its compressed powder bed surface forms almost a sphere in both Teflon grades.

3.2. Physical characteristics of the DDRS

Fig. 4 and Table 2 show the relationship between the compression force and crushing strength of the DDRS. The crushing strength of the DDRS was proportional to the compression force in both Teflon grades. A linear relationship could be seen between the 49 N/punch and 294 N/punch, however, over 294 N/punch, a linear relationship could not be seen in the case of TE-914-J. Fig. 5 shows the dissolution characteristics of DDRSs and core tablets with and without AEA coating. The core tablets with AEA coating quickly released the riboflavin in acidic conditions but did not release the riboflavin in neutral conditions. The core tablet without AEA coating (plain core tablet) released the riboflavin quickly in neutral (pH 6.8) conditions. All of the DDRSs including the most fragile one (crushing strength of 0.25 N) did not release riboflavin under either pH conditions. Due to the strong hydrophobicity and good compressibility of Teflon powder, DDRSs continuously maintained their shapes and penetration of dissolution media did not occur. Table 3 shows the effects of soaking on the crushing strength of the DDRS in JP first fluid and JP second fluid with surfactant. Soaking in the test media did not affect the crushing strength of the DDRS. In the disintegration test, DDRSs with a crushing strength of over 0.66 N did not disintegrate for up to 6 h, while the DDRS with a crushing strength of 0.25 N disintegrated in only 0.6 h (Table 2). DDRSs with a crushing strength of over 0.66 N were chipped off at the edges, but the fissure did not expand and the disintegration test media did not penetrate into the DDRSs.

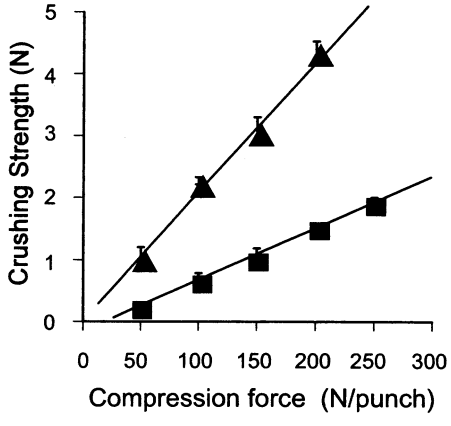

Fig. 4. Relationship between compression force and crushing strength of DDRS. Each plot shows mean ± S.D. ($n = 3$). Symbols: (■) DDRS using Teflon powder TE-914-J, (▲) DDRS using Teflon powder TE-820-J. Solid lines represent the regression lines.

Two major factors affect the process of disintegration of conventional tablets in the disintegration test and the dissolution test. One is the penetration of test media into the tablets (Ferrari et al., 1996). Once it penetrates into the tablets, the test media dissolves the ingredients, loosens the intermolecular bonding strength, and causes swelling of the disintegrant. The other is the mechanical destructive force applied to the tablets. In the disintegration test, the forces were applied to the tablets from the disk and the bottom of the basket-rack assembly. DDRS with a crushing strength of 0.25 N was disintegrated by the force. In the dissolution test, the destructive force was applied to the tablets from the stirred dissolution media, but the force was too weak to disintegrate the DDRSs.

Table 2
Mechanical properties of DDRS ($n = 3$)

Teflon grade	TE-914-J					TE-820-J			
Compression force (N/punch)	49	98	147	196	245	49	98	147	196
Crushing strength									
Mean (N)	0.25	0.66	1.01	1.50	1.89	1.08	2.22	3.04	4.28
S.D.	0.04	0.11	0.15	0.06	0.15	0.10	0.06	0.20	0.15
Thickness (mm)	5.3	4.8	4.8	4.6	4.5	4.0	3.6	3.4	3.3
Disintegration time									
Mean (h)	0.6	>6	>6	>6	>6	>6	>6	>6	>6
S.D.	0.6								

3.3. In vivo test

Riboflavin is naturally present in the human body and constantly excreted in urine. Therefore, in order to determine the amount of riboflavin in urine released from the DDRS, the basal riboflavin excretion needed to be subtracted. Fig. 6 shows the control riboflavin excretion rates measured in two subjects who were fed a low-riboflavin breakfast. The meals were found not to affect the riboflavin excretion rates, and the fluctuation range of riboflavin excretion was not more than 10 μg/h in both subjects. Thus, the riboflavin excretion level was confirmed not to fluctuate greatly. Therefore, the riboflavin excretion rate just before DDRS administration was used to calculate the actual increase in excretion rate.

In the first test under fed conditions, DDRSs with a crushing strength of 1.89 N (CS-1.89 N) were administered to six subjects after breakfast. Obvious increases in riboflavin excretion were detected in two of these six subjects (Fig. 7, Fed CS-1.89 N). The above findings suggest that the rapid increase of riboflavin in urine demonstrates a crushing of DDRS in the stomach. Based on the results of in vitro studies it is considered that the gastric fluid does not penetrate into the DDRS unless the Teflon outer layer is crushed. Next DDRSs with CS-1.50 N were administered to four subjects who did not crush DDRSs with CS-1.89 N in the first test, and all four crushed the more fragile tablet (Fig. 7, Fed CS-1.50 N). Conversely, the other two subjects who had crushed the DDRSs with CS-1.89 N in the first test, took the DDRSs with CS-3.04 N, and none of them were able to crush the harder DDRSs (Fig. 7, Fed CS-3.04 N).

In the first test under fasting conditions, none of the five participating subjects crushed the DDRSs CS-1.89 N (Fig. 7, Fasting CS-1.89 N). Next DDRSs CS-1.50 N were administered to all five subjects, and two of the subjects were able to crush them. These results showed that the human stomach had the potential force to crush tablets that have a crushing strength of 1.89 N under fed conditions and 1.50 N under fasting conditions (Fig. 8).

As the core tablet was coated with AEA, it released the marker drug in the stomach but not in the small intestine or lower part of the GI tract. Even if the core tablet released riboflavin in the lower small intestine or colon, we know that

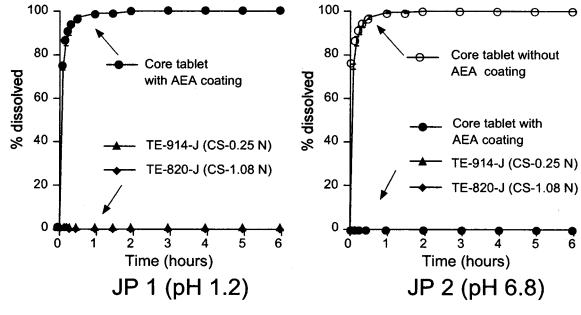

Fig. 5. Dissolution profiles of riboflavin from core tablets and DDRSs. Each plot shows mean ± S.D. ($n = 3$). Symbols: (●) core tablet, (○) core tablet without AEA coating, (▲) DDRS CS-0.25 N, (◆) DDRS CS-1.08 N.

Table 3
The effect of soaking time on the crushing strength of DDRS, mean ± S.D. ($n = 3$)

Teflon grade	TE-914-J		TE-820-J	
Compression force (N/punch)	49	245	49	196
Crushing strength (N)				
Initial	0.25 ± 0.04	1.89 ± 0.15	1.08 ± 0.10	4.28 ± 0.15
6 h in JP 1	0.27 ± 0.07	1.99 ± 0.11	1.01 ± 0.15	4.48 ± 0.25
6 h in JP 2 with surfactant	0.29 ± 0.05	2.03 ± 0.06	1.11 ± 0.11	4.44 ± 0.37

riboflavin absorption at this site would be small due to the absorption site specificity (Levy and Jusko, 1966). Thus, we can be reasonably sure that the DDRS crushing took place in the stomach when a rapid increase of riboflavin excretion is observed.

4. Discussion

Onset time of urinary riboflavin excretion is considered to represent the time to riboflavin release from dosage forms. After administration of DDRSs, a significant increase of riboflavin excretion was detected in 1–2 h or longer sampling period in all subjects (Fig. 7, Fed CS-1.50 N). When all subjects were administered only the core tablets with AEA coating, they excreted riboflavin in urine in 1 h after administration (data not shown). Consequently, even in the DDRS with lowest mechanical strength, it took a longer time to release riboflavin than the core tablet. The rapid transfer of riboflavin may reduce the bioavailability of it, because the absorption site of riboflavin is restricted in the proximal region of the small intestine via saturable transport mechanisms (Levy and Jusko, 1966). In this study, all subjects showed detectable urinary riboflavin excretion even after administration of immediate release core tablets in the pre-study administration to exclude a subject with gastric subacidity. It was concluded that analyzing urinary riboflavin excretion is an appropriate means to detect a crush of DDRS in the stomach.

The results of this report suggest that the destructive force of stomach in fed conditions is stronger than that in fasting conditions. The DDRS is considered to be crushed by receiving the contractile force directly from the gastric wall because the gastric contents present are only the gastric juice under fasting conditions or cooked rice and gastric juice under fed conditions. These contents are too soft for the DDRS to be crushed by colliding against them. Therefore direct press of gastric wall crushes DDRS in fed and fasting conditions.

The DDRS was crushed during gastric contractile motility, and the time required for DDRS crushing was affected by the gastric motility phase. In the gastric motility phase, constant contraction continues under fed conditions. During this period, solids with diameters of over 2 mm cannot pass though the pylorus. Then, the motility shifts from the fed mode to the fasting mode. In the fasting mode, the motility in the stomach occurs in 2-h cycles, each consisting of three phases. Phase I is a quiescent period, phase II is a period of irregular and gradually increasing contractions, and phase III is a period of intense contractions. The powerful contractions during phase III called housekeeper waves, carry the remaining solids with diameters of over 2 mm to the small intestine (Davis et al., 1986).

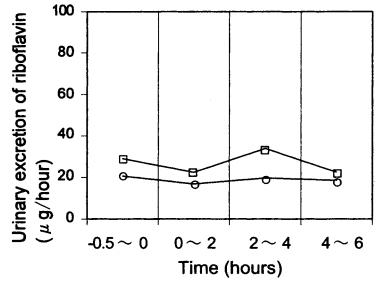

Fig. 6. Urinary excretion of riboflavin after a low-riboflavin breakfast. Symbols: (□) subject 1, (○) subject 2.

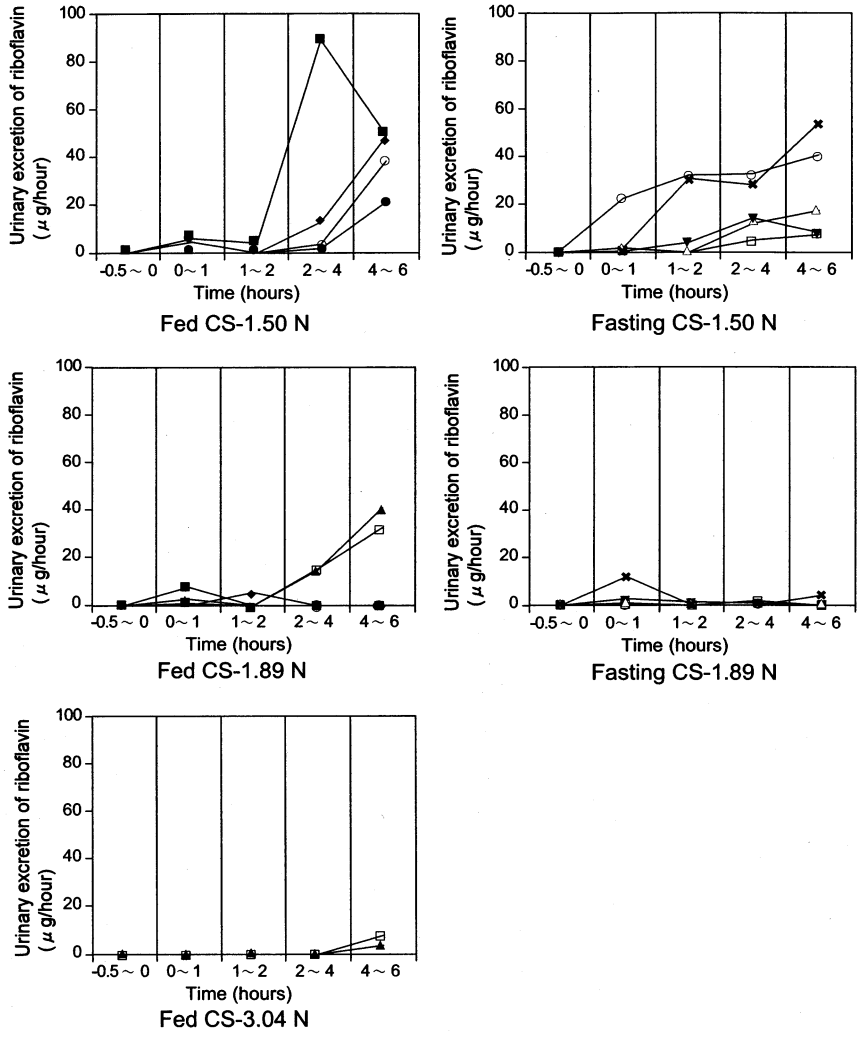

Fig. 7. Urinary excretion of riboflavin after administration of DDRS under fed and fasting conditions (with background correction). Symbols: (□) subject 1, (○) subject 2, (■) subject 3, (●) subject 4, (▲) subject 5, (◆) subject 6, (△) subject 7, (▼) subject 8, (X) subject 9.

Our DDRS has no ability to show the position in the stomach where the crushing of the DDRS takes place. However, gastric contents are normally agitated by contractile activity in antrum and contractile force in antrum is relatively stronger than other parts of stomach in dogs (Stemper and Cooke 1975). Consequently, DDRS is considered to receive the strongest contractile force in antrum in human.

Under fasting conditions, even if the contractile force in stomach is strong, the contractile activity object is to empty gastric residual contents and the pylorus is open during this period. When strong contraction take place, it moves to the antrum; the effect of such contraction is mainly to squeeze out the DDRS through the pylorus. Thus, the DDRS cannot receive an effective mechanical destructive force from gastric wall in the fasting conditions. However, under fed conditions, the pylorus is closed and the contractile activity object is to grind solid meal (Meyer et al., 1981). Therefore DDRS would be crushed in stomach

like solid meal. This activity provides the DDRS with a stronger destructive force from the gastric wall than in the fasting mode, and this could be the main reason that two of the six subjects crushed CS-1.89 N.

General controlled-release tablets receive two types of destructive force in stomach (Katori et al., 1995). One is pressure from gastric wall, the other is the friction between the surface of the tablets and gastric wall or gastric contents. The former is suitable to be evaluated by the DDRS. This force may cause dose dumping of non-erodible dosage forms like enteric-coated tablets, wax-matrix tablets, enteric-coated capsules, and colon targeted devices. However, the DDRS is not suitable for evaluating the friction. This force is weak but, for example, the surfaces of erodible hydrogel tablets are scrubbed by the force.

The destructive force in the human stomach was evaluated using the DDRS. With some modifications, the DDRS could also be applied to other parts of the GI tract in man and experimental animals. Information on destructive forces in the GI tract of man and experimental animals would be useful to consider corresponding differences in bioavailabilities.

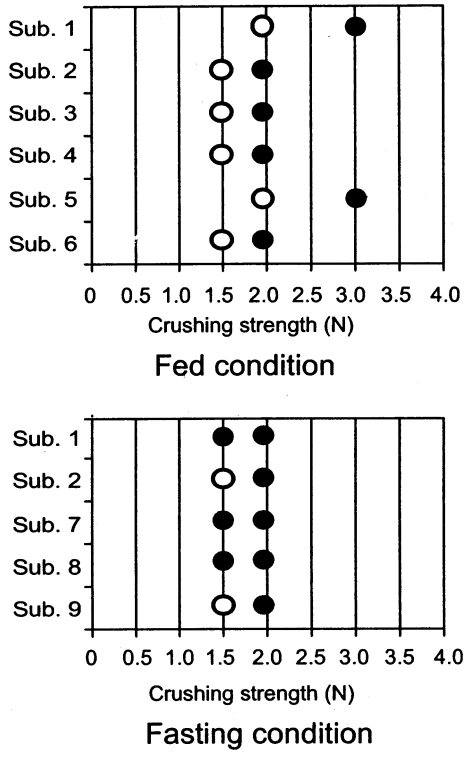

Fig. 8. Crushing strength in human stomach under fed and fasting conditions. Symbols: (○) crushed, (●) not crushed.

5. Conclusions

We prepared a dosage form which can evaluate the mechanical destructive force in the human stomach. The in vivo study showed that the human stomach potentially imparts a mechanical destructive force of 1.89 N to all dosage forms under fed conditions. This value can be used not only to recognize differences between in vitro and in vivo dissolution properties of dosage forms, but also as criteria for dose dumping in developing controlled-release dosage forms.

Acknowledgements

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