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Evaluation of the mechanical destructive force in the stomach of dog

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Abstract

Orally administered dosage forms receive a destructive force in the gastrointestinal (GI) tract due to peristalsis. In this study, the destructive force was measured with a 'destructive force-dependent release system' (DDRS). DDRS is a press-coated tablet with an extremely brittle outer layer composed of highly hydrophobic Teflon® powder, which is molded with a weak compression force. Teflon® powder forms a porous but water-impermeable layer around the core tablet. A marker drug contained in the core tablet is released only when the tablet receives a force larger than its pre-determined crushing strength. A comparison of the physiological conditions in the GI tract of dogs with those of humans, including the destructive force against tablets in the stomach, helps us to understand their difference in bioavailability of oral dosage forms. With DDRS, it is possible to evaluate the destructive force of both human and dog stomach using the same method. Therefore, the destructive force data from human and dog can be directly compared. The destructive force in the dog stomach was evaluated to be 3.2 N, which was considerably stronger than that of humans. © 2001 Published by Elsevier Science B.V.

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

1. Introduction

Dogs have been widely used as animal models to evaluate the bioavailability of a new drug substance or new oral dosage forms in preclinical studies. For efficient dosage form development, prediction of in-vivo drug release in humans from the data of dogs is desirable. Knowledge on the physiological conditions in the gastrointestinal (GI) tract of humans and dogs that may affect in-vivo drug release is essential for such predictions. Among the GI factors, many studies have been conducted on pH conditions (Itoh et al., 1986; Chan et al., 1990; Mojaverian et al., 1991) and GI transit rates of dosage forms (Meyer et al., 1979; Davis et al., 1986; Kenyon et al., 1994). Recently, some studies have investigated the effect of the mechanical destructive force in the GI tract on in-vivo drug dissolution of oral solid dosage forms (Katori et al., 1995; Shameem et al., 1995).

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This information is important to optimize oral dosage forms, especially sustained release dosage forms and colonic delivery dosage forms (Steffensen and Pedersen, 1986). It is necessary for those dosage forms to keep their original shape until they reach the target site. For the sustained release dosage forms, a sudden disintegration by the peristalsis in the GI tract results in what is called dose dumping. Dose dumping is potentially dangerous, particularly that of a once-daily sustained release formulation as a large dose is contained in one unit. For colonic delivery dosage forms, disintegration at an unintended site impairs their efficacy. However, the available amount of information on this mechanical destructive force is still limited. Moreover, very few studies have focused on the difference of mechanical destructive force between humans and dogs.

A manometer (Stanghellini and Malagelada, 1983) was reported as a method to monitor the GI contractile waves in healthy volunteers. A strain gauge is a common method to study the contractile activity in the GI tract of dogs. However, manometry and strain gauge methods were not suitable to evaluate the mechanical destructive force that was applied to the dosage forms in the GI tract.

A destructive force-dependent release system (DDRS) has been developed to evaluate the GI mechanical destructive force, especially the crushing force in the GI tract (Kamba et al., 2000). Teflon powder was found to be ideal for the DDRS as it is very hydrophobic, and it does not dissolve in any media. In addition, it can be easily molded into a brittle matrix with a small compression force. The matrix is porous but water-impermeable because of the hydrophobicity of Teflon®. Based on these characteristics, it was possible to design a dosage form that releases a marker drug only when the tablet received a force larger than its predetermined crushing strength. The DDRS is a press-coated tablet composed of a core tablet containing a marker drug and Teflon® outer layer.

The DDRS has many advantages:

1. the DDRS can be applied to both humans and dogs with minimal modifications;
2. results derived from DDRS administration can be compared directly between humans and dogs;
3. the shape and size of the DDRSs are similar to actually marketed tablets;
4. the crushing strength of the DDRS can be well controlled;
5. the soaking time in the GI fluid does not affect the crushing strength.

The mechanical destructive force in the stomach of human was previously evaluated to be 1.9 N using the DDRS. In this study, the destructive force in the stomach of beagle dogs was evaluated using a modified DDRS.

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). Sulfamethizole (SMZ), sulfisoxazole (SIX) and cefradine (CFD) were purchased from Sigma Chemical (USA). Cefalexin (CLX) was purchased from Wako Chemicals (Japan). Polysorbate 80 was purchased from Kao (Japan). Gelatin capsules (size #00) were purchased from Matsuya (Japan). Pentagastrin was purchased from Sigma Chemical (USA). Solid meal (Lab ration 4360) for dogs was purchased from Purina Japan (Japan).

2.2. Structure of the DDRS and process of its manufacture

The structure, composition and process of manufacture of the DDRS for human stomach have been described previously (Kamba et al., 2000).

The structure of the DDRS for dog stomach was shown in Fig. 1. The DDRS for dog stomach is essentially same as the DDRS for human stomach. However, some modification was made in the DDRS for dog stomach as follows:

1. the marker drugs were changed from riboflavin to sulfamethizole, sulfisoxazole, cefradine and cefalexin to make HPLC assay easy;
2. only one grade of Teflon powder (TE-820-J) was used, because the destructive force of dog

stomach was estimated to be stronger than that of human from preliminary experiment, and TE-820-J was suited to prepare the harder outer layer;

3. four DDRSs, having different crushing strengths with different marker drugs, were filled into a gelatin capsule.

2.3. Measurement of crushing strength of the DDRS

The crushing strength of the DDRS was determined in Japanese Pharmacopoeia (JP) XII first fluid (pH 1.2) at 37 °C using a Rheometer (Fudohkogyo, NRM-2010J-CW, Japan). The DDRS was pressed against the adapter in the direction of the diameter in a manner similar to measuring radial hardness of tablets with general tablet hardness testers.

2.4. Dissolution test, disintegration test and soaking test

Disintegration tests for the core tablets A, B, C, and D were carried out for 6 h, and the tests for the DDRSs were continued for up to 24 h at 37 °C in JP XII first fluid (pH 1.2) and second fluid (pH 6.8), using a JP XII disintegration apparatus with disks. The crushing strength of the DDRS was measured after soaking in dissolution test fluid. The tests were carried out for 6 h at 37 °C in 100 ml of JP XII first fluid. Dissolution tests for DDRS by the paddle method (50 rpm, JPXII apparatus 2) were carried out for 6 h at 37 °C in 900 ml of JP XII first fluid or second fluid 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 marker drugs dissolved in the test fluid was determined spectrophotometrically.

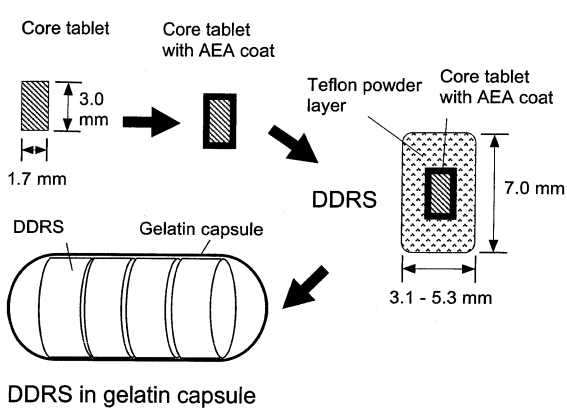

Fig. 1. Cross section of Teflon® tablet (DDRS) and scheme of the DDRS in a gelatin capsule.

2.5. In-vivo study

Four dogs (male beagle, weight 10.2–11.6 kg) were used in this study. DDRSs were administered to each dog under the fed and fasting conditions with a 1 week washout period. Three dogs used as a reference control (male beagle, weight 11.1–13.3 kg) were administered a capsule filled with all four core tablets (A, B, C, D), and the excreted amount of the marker drugs in the urine was measured. Prior to each experiment, the dogs had been fasted for 18 h with free access to water. For dogs under fasting conditions, DDRS was administered with 20 ml of water. For dogs under fed conditions, 200 g of solid meal was consumed, and 30 min after the meal, DDRS was administered to the dogs with 20 ml of water. During the experiments, the dogs were allowed free access to water.

The urine samples were collected from each dog for 24 h after the administration and the volume of collected urine was measured. The samples were stored at −80 °C until assay. The blank samples were collected from each dog the day before the administration. The pH of gastric fluid was adjusted to a low pH (pH 1.0–2.0) by pretreatment with pentagastrin (Yamada et al., 1990). Pentagastrin (12 μg/kg) was injected to muscle at 0.5 h prior to administration, and at 0, 0.5, 1, 1.5, 2, 3, 4, and 5 h after administration.

2.6. Assay for marker drugs in urine

The concentrations of marker drugs in urine were determined by HPLC. Conditions for the HPLC analysis were as follows: column, TSK-GEL ODS-80Ts (4.6 mm × 15 cm) (Tosoh,

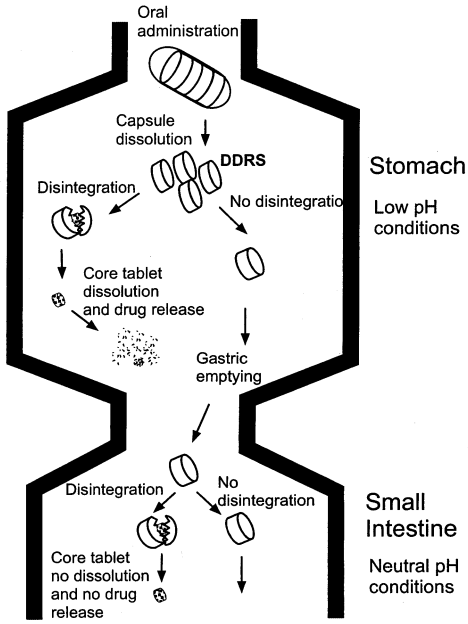

Fig. 2. Schematic diagram of the DDRS mechanism of action in stomach and small intestine.

Japan); mobile phase, 0.03% (w/v) CH_3COONH_4 buffer-acetonitrile (95:5, v/v); flow rate, 1.0 ml/min; detector, UV spectrophotometer SPD-6A (Shimadzu, Japan) (260 nm). The urine sample was centrifuged (05PR-22, Hitachi, Japan) at 3000 rpm for 5 min and 50 μl of supernatant was injected to HPLC.

2.7. DDRS mechanism of action

The action mechanism of the DDRS is shown in Fig. 2. Encapsulated DDRS is orally administered. The hard gelatin capsule protects the DDRS from destruction during the handling before administration and during its passage through the mouth and esophagus. Then, it dissolves in the stomach to release the DDRS. The DDRS receives a contraction force from the stomach wall. When the destructive force is larger than the crushing strength of the DDRS, the outer layer breaks. Then, the core tablet becomes exposed to the gastric juice. The exposure of the core tablets to the gastric juice results in an immediate disintegration of the core tablets. The marker drug is then released, absorbed, and excreted in urine. Thus, the crushing of the DDRS can be confirmed by detecting the marker drug in 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 down 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. DDRS was designed in consideration of the following physiological conditions. The gastric juice of dog is basically acidic; however, the acidity of the gastric juice may occasionally become neutral (Itoh et al., 1986). Therefore, the gastric juice was regulated to low pH conditions with the injection of pentagastrin. The pH of intestinal juice is 6.0 (4.0–7.2) (Lui et al., 1986). The gastric emptying time of the tablet (diameter of 6.0 mm) is 0.8 h under fasting conditions and is more than 10 h under fed conditions (Aoyagi et al., 1992).

Table 1
Disintegration test of core tablets

Dosage form (marker drug)		Core A[a] (SIX)	Core B[a] (SMZ)	Core C[a] (CFD)	Core D[a] (CLX)
	Test medium				
Disintegration time	pH 1.2 (JP 1st), (min ± S.D.)	4 ± 0	5 ± 0	3 ± 0	5 ± 0
	pH 6.8 (JP 2nd), (h)	>6	>6	>6	>6

$n = 3$.
[a] The core tablets were coated with AEA.

Table 2
Physical properties of DDRS

Compression force (N/punch) (Core tablet)		78 (A)[a]	118 (B)[a]	147 (C)[a]	196 (D)[a]
Crushing strength (N)	Initial	1.4 (0.1)	3.2 (0.2)	3.8 (0.1)	6.1 (0.2)
	After soaking[b]	1.7 (0.1)	3.6 (0.1)	4.2 (0.1)	7.2 (0.1)
Dissolution rate (%)[c]	pH 1.2 (JP 1st)	0	0	0	0
	pH 6.8 (JP 2nd)	0	0	0	0
Disintegration time	pH 1.2 (JP 1st)	>24 h	>24 h	>24 h	>24 h
	pH 6.8 (JP 2nd)	>24 h	>24 h	>24 h	>24 h

$n = 3$ (S.D.).
[a] The core tablets were coated with AEA.
[b] The DDRSs were soaked in JP 1st fluid at 37 °C for 6 h.
[c] Dissolved percentage after 6 h.

3. Results

3.1. Physical properties of the DDRS

Table 1 shows the results of the disintegration test of the core tablets. The core tablets coated with AEA film disintegrated immediately under acidic conditions but not under neutral conditions. Table 2 shows the relationship between the compression force and the crushing strength of the DDRS. The crushing strengths of DDRSs were controlled to 1.4, 3.2, 3.8 and 6.1 N. The effect of soaking DDRS in JP first fluid on its crushing strength is also shown in Table 2. After soaking the DDRS in JP 1st fluid for 6 h, the crushing strength was increased slightly. However, their change was negligible in the evaluation of the mechanical destructive force of the stomach. Therefore, results below and discussion are described with the values of DDRS before soaking. Table 2 shows that the DDRSs were not disintegrated for up to 24 h in the JP disintegration test. The dissolution test results for the DDRS showed that there was no release of the marker drug under acidic and neutral conditions, even for the most fragile one, with a crushing strength of 1.4 N. Due to the strong hydrophobicity and good compressibility of the Teflon® powder, the DDRSs consistently maintained their initial shapes and penetration of dissolution media into the tablets did not occur when a weak mechanical force was applied as in the disintegration test or the dissolution test.

3.2. In-vivo study

Table 3 shows the cumulative amounts of the marker drugs excreted in urine after oral administration of the core tablets to the dogs. DDRSs having a crushing strength of 1.4, 3.2, 3.8 and 6.1 N were administered to each of four beagle dogs under fed conditions. Three out of the four dogs crushed the DDRS having a crushing strength of 1.4 N and 3.2 N. No dog crushed the DDRS having a crushing strength of 3.8 N and 6.1 N (Table 4 and Fig. 3, Fed conditions). The fourth dog, D65, did not crush any DDRS. DDRSs having a crushing strength of 1.4, 3.2, 3.8 and 6.1 N were administered to each of four beagle dogs under fasting conditions. Three of the four dogs crushed the DDRS having a crushing strength of 1.4 N and 3.2 N. No dog crushed the DDRS having a crushing strength of 3.8 N and 6.1 N (Table 4 and Fig. 3, Fasting conditions). The dog, D65, did not crush any DDRS under fed and fasting conditions. Therefore, the destructive force in the stomach of D65 could be considered exceptionally weak among the dogs. These results showed that the dog stomach had a potential force to crush tablets that have a crushing strength of 3.2 N under fed and fasting conditions (Fig. 3).

4. Discussion

Very few studies have focused on the difference of mechanical destructive force between humans and dogs. A manometer (Stanghellini and Malagelada, 1983) was used to monitor the GI contractile waves in patients and healthy volunteers. Pressure-sensitive radio telemetry capsules (Coupe et al., 1991) were also reported as a method to monitor the GI contractile waves in healthy volunteers. A strain gauge is a common method to study the contractile activity in the GI tract of dogs. In manometry and strain gauge, the recorded pressure change or stress is related to the strength of contractile activity in the GI wall. Contractile activity in the GI wall is not a direct measurement of the force applied on the dosage forms. In pressure-sensitive radio telemetry capsules, the size and form of the sensors used in the studies were much larger than those of actually marketed tablets or capsules. Therefore, manometry and strain-gauge methods were not suitable to evaluate the mechanical destructive force that was applied to the dosage forms in the GI tract.

To gain a better understanding of the correlation between human and dog bioavailability, some studies have been carried out in terms of the GI pH and GI transit rate (Lui et al., 1986). In these studies, it was very important to apply the same measuring method in both species for a direct comparison. A manometer was used for measuring the GI destructive force in humans and dogs (You and Chey, 1984). However, in the dog study, anesthetization was necessary during the experiments. Thus, using a manometer is not an appropriate measuring method to evaluate the effect of the GI destructive force on the bioavailability of a dosage form.

Shameem et al. and Katori et al. adopted another approach to evaluate the GI destructive force. They used hydrophilic matrix tablets and considered the erosion rate of the hydrated matrix as an index of GI mechanical destructive force. However, since the tablets used in these studies were made from hydrophilic materials, the mechanical properties of the tablets changed with an increase in soaking time in the GI fluid. Nevertheless, their methodology is well suited for measuring the grinding or frictional force of the GI tract.

Our study showed that the mechanical destructive force in the stomach of dog was 3.2 N and that this force was stronger than that of human (1.9 N) (Kamba et al., 2000). This suggests that dog is not an appropriate animal model to evaluate in-vivo drug release from the dosage forms that release rate is influenced by the agitation in the GI tract. An example of such dosage form is the hydrogel matrix tablet. Regarding the other differences in the GI tract conditions between dog and human, it is known that the pH of dog stomach is unstable, and the transit time in the dog GI tract is shorter than that of human. We should recognize these differences when we use dogs to evaluate oral dosage forms, especially the sustained release dosage forms.

Our previous study showed that the destructive force in the stomach of human under fed conditions was 1.9 N, and it was 1.5 N under fasting conditions (Kamba et al., 2000). Therefore, in the stomach, the destructive force is stronger under fed conditions than that under fasting conditions in human. However, this study suggested that the destructive force in the stomach of beagle dogs was equivalent under fed and fasting conditions. The reason for this discrepancy between humans and dogs may be due to the selection of inappro-

Table 3
Urinary excretion of marker drugs

Dosage form (marker drug)	Core A[a] (SIX)	Core B[a] (SMZ)	Core C[a] (CFD)	Core D[a] (CLX)
Drug excretion[b] ± S.D (mg)	1.4 ± 0.2	2.5 ± 0.6	0.7 ± 0.3	1.3 ± 0.5

$n = 3$.

[a] The core tablets were coated with AEA. Each core tablet contained 5 mg of marker drug.

[b] Cumulative amount of marker drugs in urine within 24 h.

Table 4
Excretion amounts of marker drugs after administration of DDRSs under fed and fasting conditions

Dog number	Diet condition	Crushing strength of DDRSs			
		1.4 N (mg) (SIX)[a]	3.2 N (mg) (SMZ)[a]	3.8 N (mg) (CFD)[a]	6.1 N (mg) (CLX)[a]
D 24	Fed	1.2	2.3	n.d.	n.d.
	Fasting	1.0	1.9	n.d.	n.d.
D 25	Fed	0.6	1.8	n.d.	n.d.
	Fasting	0.8	1.0	n.d.	n.d.
D 65	Fed	n.d.	n.d.	n.d.	n.d.
	Fasting	n.d.	n.d.	n.d.	n.d.
D 66	Fed	0.4	1.3	n.d.	n.d.
	Fasting	1.1	2.2	n.d.	n.d.

n.d.: not detected.
[a] Marker drug contained in the DDRS.

priate crushing strengths of the DDRS administered to the dogs. With more precise control of crushing strength between 3.2 N and 3.8 N, the destructive force under two diet conditions would be determined more precisely. However, due to the limitation of the methodology, we cannot differentiate between these two values.

Another factor to consider is the pharmacological effects of pentagastrin on the gastric contractile motility. In this study, pentagastrin was used to control the pH of gastric fluid under fasting conditions. Administration of pentagastrin was necessary to make sure of the AEA film dissolution in the stomach, because the dog gastric pH varies widely. Pentagastrin promotes the secretion of gastric acid. However, other pharmacological effects on the motility of the stomach are not completely established (Kelly, 1970; Fox et al., 1983). Some studies suggest that pentagastrin changes the gastric motility from the interdigestive pattern to the digestive pattern (Bech and Andersen, 1984). Therefore, the result of this study under fasting conditions may not reflect the natural fasting gastric conditions.

However, for the results under fed conditions, the pharmacological effect of pentagastrin could be negligible because the gastric motility is already in the digestive pattern. Despite these uncertainties regarding pentagastrin administration, it could be concluded that the maximum destructive force of the dog stomach is 3.2 N, regardless of the diet condition.

The pH of gastric fluid was adjusted by pretreatment with pentagastrin in the fed and fasting conditions. The pH of gastric fluid soon becomes low (pH 1.0–2.0) in the fasting conditions by the pentagastrin pretreatment (Yamada et al., 1990). In the normal fed conditions, the gastric pH becomes pH 4–5 soon after feeding then becomes low (pH 1.0–2.0) in 1 h (Itoh et al., 1986). Therefore, the gastric pH would be low enough to dissolve AEA coating film during the test period.

Four marker drugs were used in the dog stomach study. The cumulative urinary excretion amounts of the four marker drugs from the four core tablets with AEA coating were studied using three control dogs (Table 3). The urinary excretion ratios of four marker drugs were 60–100% in human (Brogard et al., 1975; Slywka et al., 1976;

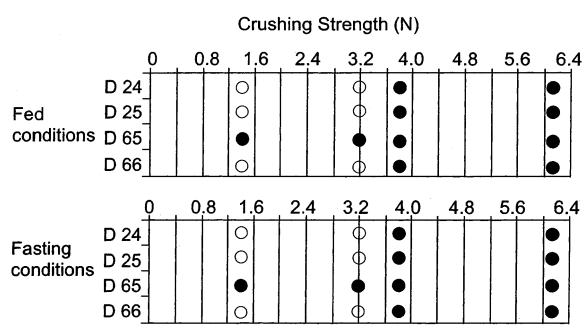

Fig. 3. Destructive force in dog stomach. D24, D25, D65 and D66 represent the code of dogs. Symbols: (○) crushed, (●) not crushed.

Hendrix et al., 1993; Yoshitomi et al., 1993). The data in Table 3 show that the urinary excretion ratios of these marker drugs of the dogs are smaller than that of humans. However, the excreted amounts of the marker drugs were high enough to detect their absorption in dogs. Some values of the excreted amount of the marker drugs in Table 4 showed more deviation than expected from the statistical data in Table 3. This deviation could be explained by the inter-individual variation, because the dog groups used in Table 3 and Table 4 were different dog groups.

The DDRS system will be applied to evaluate the destructive force in the small intestine with some modifications. The DDRS for stomach can be easily changed into a DDRS for small intestine by removing the AEA coating from the core tablet and coating the capsule containing the DDRS with enteric films. The information on the destructive force in the stomach and the small intestine would be useful for developing the sustained release and colonic delivery dosage forms.

5. Conclusions

Our study showed that the dog stomach potentially has a mechanical destructive force of 3.2 N. The information gathered in this study will help us account for the differences in bioavailability between human and dog.

Acknowledgements

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