Effect of Destruction Force on Drug Release from Multiple Unit Controlled Release Dosage Forms in Humans

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Purpose. This study examined the effects of mechanical destructive forces on drug release from controlled release (CR) multiple unit dosage forms in vitro and in vivo and their colonic release, using two CR granules of acetaminophen, AG and BG, which differed in hardness (AG was hard and BG was soft), but which did not depend on agitation speed or pH for their release.

Methods. *In vitro* release rates were determined using several official methods and the rotating dialysis cell method. Granules were administered to healthy volunteers under fasting and fed conditions.

Results. Both granules showed similar release rates under mild destructive conditions in official dissolution tests, but BG showed a faster release rate in the rotating dialysis cell method. In the fasting state, the drug absorption-time profiles of AG and BG were almost equal. In the fed state, the drug release rate of BG increases whereas that of AG is almost equal to the fasted state. The food effect on BG could be caused by an increase in the mechanical stress of the GI tract due to food intake judging from the findings *in vitro* and in dogs. The colonic release from multiple unit CR products was larger than that from single unit ones.

Conclusions. *In vivo* release of drug from a multiple unit CR product that is structurally weak is affected by mechanical stresses, which differ among human subjects but are increased by food ingestion. Colonic release from multiple unit CR products is larger than that from single unit products.

KEY WORDS: controlled release; GI Mechanical destructive forces; colonic release; *in vitro* dissolution tests.

INTRODUCTION

To improve oral dosage forms, factors affecting drug release/absorption in the gastrointestinal (GI) tract should be clarified. *In vitro* drug release systems that adequately predict *in vivo* drug release facilitate this development. Systems should be developed considering GI factors such as pH, bile acid concentration, viscosity, volume of water, GI residence time and agitation intensity. However, the effects of physical factors on *in vivo* dissolution such as the hydrodynamic flow of GI fluid and mechanical destructive forces due to GI motility have hardly been investigated. In our previous reports, we demonstrated that the destructive force in the GI tract plays an important role on the drug release from an erodable single unit CR dosage form (2). However, CR products in multiple unit dosage forms have been used preferentially, because their gastric emptying is less variable than single unit products. However, the effect of the GI tract's destructive force on drug release from multiple CR unit dosage forms has not been clarified.

This study investigated the effect of mechanical destructive forces in the GI tract based on an *in vitro/in vivo* comparison of drug release and tried to develop appropriate *in vitro* model of dissolution. We prepared two different types of CR acetaminophen (paracetamol) granules: AG and BG, which differed in hardness (AG was stronger and BG was weaker). However, neither form depended on agitation speed or pH for drug release.

MATERIALS AND METHODS

Dosage Forms

Two types of CR spherical granules were prepared. Both granules were 1 mm in diameter and contained acetaminophen. Their structure and components are shown in Fig. 1. The core of AG was an insoluble matrix in which acetaminophen particles were scattered, whereas the core of BG was made of a soluble sugar particle (nonpareil, 24–32 mesh) which was covered with a drug layer. Therefore, the hardness of BG would decrease in an aqueous media as the core dissolved.

In Vitro Release Test

Release tests were carried out at 37°C using 0.05M sodium acetate buffer (pH 4.0), JP XII first (pH 1.2), or second fluids (pH 6.8). The release rates were determined in 900 mL of test medium by JP XII paddle (10–100 rpm), rotating basket (25–100 rpm) and flow-through cell methods (0.9–44.5 cm/min) using a small cell measuring 12 mm in diameter. The rotating dialysis cell method (6) was also used, in which twenty polystyrene beads (6.5 mm diameter and specific gravity 1.05 g/cm^3) were placed in a cell made from a cellulose tube (Spectra/Por® membrane 6, Spectrum Medical Industries, Inc., USA). No test medium was added to the cell. The cell was rotated at 5 rpm horizontally in 700 mL of medium at 37°C. JP XII 2nd fluid was used for all dissolution tests except the pH study. The effects of pH and polysorbate 80 (0.5%) on drug release were investigated by the paddle method. The amount of acetaminophen released in the test fluid was spectrophotometrically determined. All tests were carried out in duplicate or triplicate.

In Vivo Test

Six healthy volunteers ranging from 25 to 52 years in age participated in this study. Written informed consent was obtained from each volunteer prior to the study. Test granules were administered to subjects together with 200 mL of water after an overnight fast or immediately (within 5 min) after ingesting a standard breakfast (1775 kJ) consisting of two slices of bread, 20 g butter, one boiled egg, half a cucumber and 200 mL of milk. Food was allowed 4 hrs after drug administration with free access to water. Saliva samples were collected from each subject at set intervals for up to 24 hrs and stored at −20°C until assay. Test granules were administered with at least a 1-week interval according to a cross-over design. All subjects were also administered 100 mg of acetaminophen solu-

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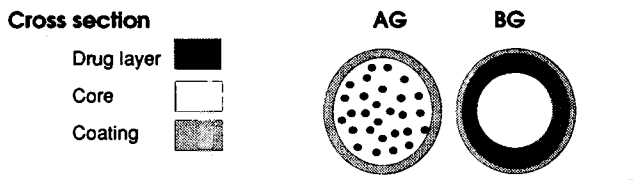

Components (mg)	AG	BG
Drug layer		
Acetaminophen	100.0	100.0
Hydroxypropylcellulose	-	20.0
Core		
Cellulose	400.0	-
Sugar particle (Nonpareil, 24-32 mesh)	-	66.7
Coating		
Ethylcellulose	22.5	2.9
Hydroxypropylmethylcellulose	2.5	0.3
Total weight	525.0	189.9

Fig. 1. Cross-sections and composition of controlled release acetaminophen granules AG and BG.

tion orally after an overnight fast. The concentrations of acetaminophen in saliva were determined by high-performance liquid chromatography as previously reported (1).

Drug release in humans following oral administration was calculated by the constrained deconvolution method of Verotta et al. (7), in which p.o. solution data were used for weight function. The weight function of deconvolution was determined using pharmacokinetic model parameters; these were fitted in to a compartment model using the MULTI (8) program, in which Akaike's information criterion was used for model selection.

RESULTS

In Vitro Drug Release

The results of *in vitro* drug release tests are shown in Fig. 2. *In vitro* drug release rates of the two types of granules were almost equal and were virtually unaffected by the agitation intensity using official dissolution test methods such as the paddle, rotating basket, and flow-through cell method. When the JP disintegration test method was used for the dissolution test, the dissolution profiles of AG and BG were the same as

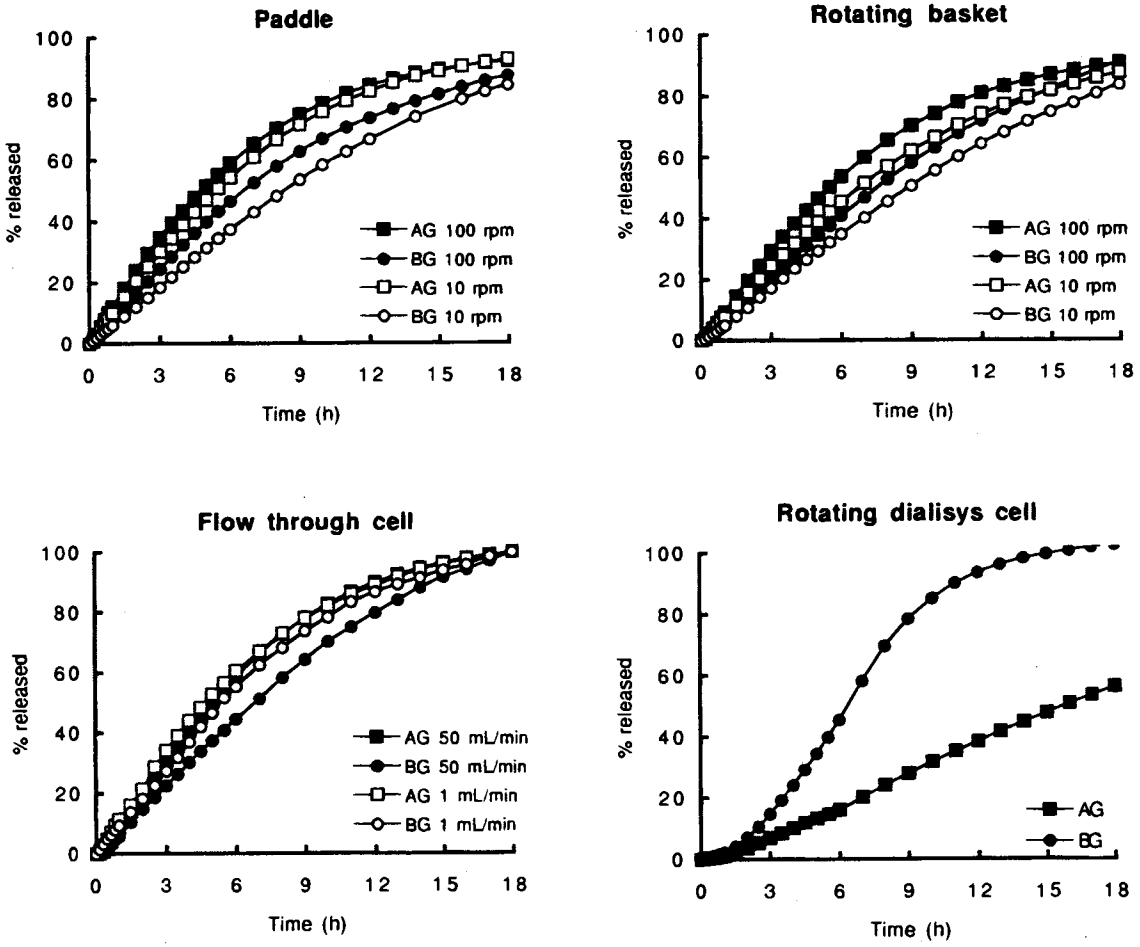

Fig. 2. Dissolution profiles of acetaminophen granules AG and BG by using different dissolution test methods.

that for the paddle method (data not shown). Their dissolution was unaffected by the addition of a surfactant (0.5% polysorbate 80) and by changes in pH (data not shown).

However, when the rotating dialysis cell method was used, dissolution rates differed between AG and BG. Drug release from BG rapidly increased after 2hr. This phenomenon seemed to be caused by the destruction of BG which became weaker as the sugar in the granule core dissolved. The granules were rolled in a cell containing polystyrene beads to create mechanical stress. In this method, the granules and beads in the cell became wet, because of the small amount of medium penetrating the dialysis membrane. When more than 0.2 mL of medium was added the cell, the dissolution rate of AG increased considerably and became similar to that of BG (data not shown).

In Vivo *Drug Release*

The mean drug levels in human saliva after oral administration of AG and BG are shown in Fig. 3a,b. The model-independent parameters are shown in Table I. C_{max} for BG in the fed state was significantly larger than that in the fasting state.

The mean release-time profiles of AG and BG in humans are shown in Fig. 3c,d. Drug absorption-time profiles of AG under fasting and fed conditions were almost equal. However, the drug release characteristics of BG were quite different between the two conditions; the mean drug release time in the fed state was faster than that in the fasting state. Four of the six subjects showed a sudden elevation in drug release 2–3 hr after administration of BG with food (Fig. 4). The remaining two subjects did not show it although they showed a slightly larger absorption rate in the fed state than in the fasting state. This fact suggests that there are large differences between individuals with regard to the destructive force in the GI tract as shown in our previous reports (2).

In Vitro/In Vivo *Correlations*

Comparing *in vitro* and *in vivo* drug release, the individual *in vivo* release rate of acetaminophen of AG and BG in the fasting state were equal to or lower than the *in vitro* release rate at 10 rpm of the paddle (Fig. 4). Most of the individual release profiles of AG were observed between the *in vitro* release rate at 10 rpm of the paddle and that by the rotating dialysis cell method. Release of BG in the fed state was equal to or higher than the *in vitro* release rate by each method. Steep increases in the *in vivo* release in the fed state could not be predicted from any of the official dissolution tests; except the rotating dialysis-cell method which showed accelerated BG release.

DISCUSSION

In the present study, food effects were noted for BG but not for AG. The *in vivo* drug release of BG suddenly increased during the second hour after administration in the fed state

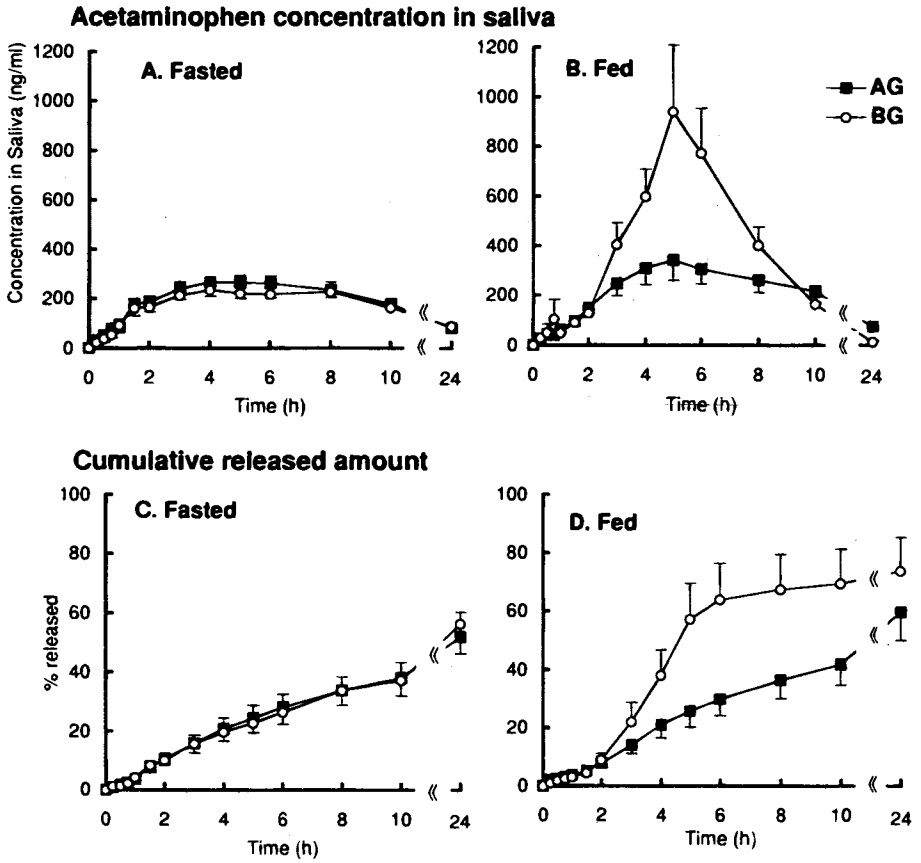

Fig. 3. Mean (n = 6) of saliva concentration and cumulatively released amount of acetaminophen in humans after administration of AG and BG. Vertical lines show SE.

Table I. Pharmacokinetic Parameters of Acetaminophen in Humans (mean ± SE, n = 6)

	Fasted		Fed	
	AG	BG	AG	BG
AUCt,ng · h/ml	3949 ± 279	3643 ± 156	4255 ± 777	5520 ± 1040
C_{max},ng/ml	292.8 ± 26.2	268.2 ± 24.9	382.2 ± 70.8	1010.0 ± 254.0*
T_{max},h	5.17 ± 0.65	5.33 ± 0.88	5.67 ± 0.56	4.83 ± 0.31
MRT,h	9.54 ± 0.29	9.94 ± 0.75	9.28 ± 0.44	6.78 ± 0.11*

Note: AUCt: area under the plasma concentration-time curves from zero to 24 h. *Significant difference ($p < 0.05$) between fasted and fed condition.

(Fig. 3d), whereas that of AG did not increase (Fig. 3c). In general, food effects on drug absorption are considered caused by an increase of bile acid secretion, the lipids in food, and a delay in the GI transit time (3). However, the effect of bile acid on drug release from AG and BG might be negligible, because *in vitro* dissolution was not affected by the addition of a surfactant to either granule. It was concluded that the food effect on BG was caused by mechanical stress in the GI tract.

AG and BG granules were both coated with ethylcellulose-HPMC membrane, but the cores of the granules were different. The core of AG was an insoluble matrix, whereas the core of BG was made with sugar particles which was easily dissolved in water. The hardness of BG was reduced after the core dissolved. Mizumoto et al., who supplied the AG and BG granules, used a rheometer to measure the hardness of the granules after soaking them for 30 mins in dissolution test medium and reported that granule hardness was 164 g for AG and 71 g for BG (4). This decreased hardness of BG can explain its accelerated *in vivo* drug release under the highly destructive conditions caused by food. In the fasting state, the mechanical destructive force was not sufficient to disintegrate the AG and BG granules. Pressure

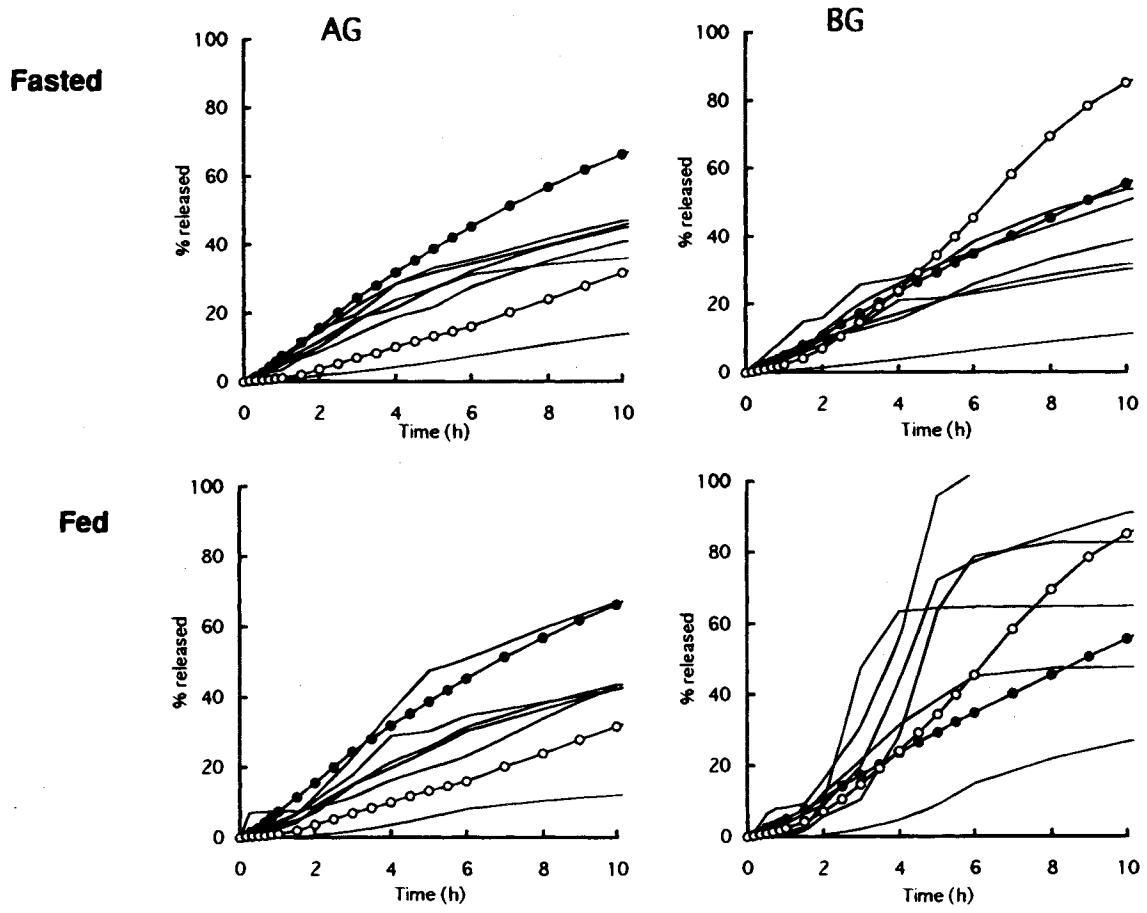

Fig. 4. Comparison of *in vitro* dissolution profiles and *in vivo* individually released amount of acetaminophen. Closed circles show *in vitro* drug release at 10 rpm of paddle. Open circles show *in vitro* drug release at 5 rpm of rotating dialysis cell. Solid lines show individual drug release in humans.

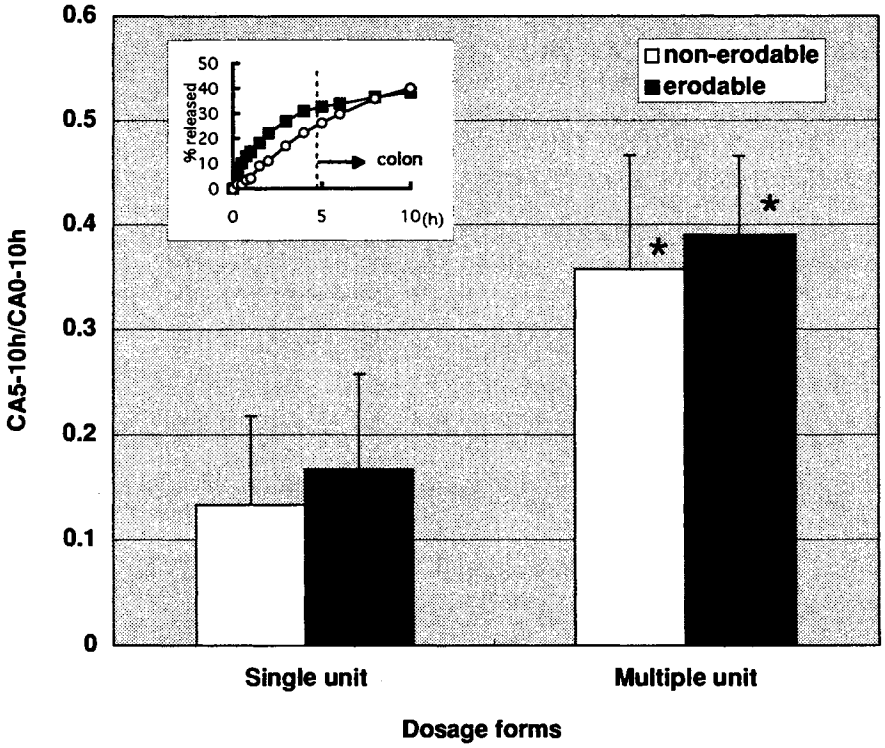

Fig. 5. Mean and SD of drug amount released in the colon in fasting state. Rate of drug release in the colon was represented as an amount released from 5 to 10 hr vs. that from 0 to 10 hr. Data of single unit dosage forms were brought from ref. 2. *significantly different ($p < 0.01$) from single unit

on the granules in the GI tract was estimated being less than 71 g in the fasting state. However, the mechanical destructive force in the fed state was not sufficient to disintegrate the AG granules, but could disintegrate the BG granules; the pressure in the fed state was estimated between 70 and 164 g. The elapsed time until a sudden elevation of BG release in the fed state might be the time requested to decrease the strength of the core to the critical level of crushing. These possible explanations can be supported by the canine study by Mizumoto et al. (4). They also reported that the drug absorption rate of BG was larger than that of AG in dogs in the fed state, and most of the BG granules recovered from the dogs' GI tract were cracked, while the AG granules were not.

In our previous studies using an erodable single unit CR dosage form that was sensitive to mechanical stress, there was little effect from food on *in vivo* drug release (2). What caused the differences between these studies? Differences in findings may be related to the difference in the acceleration mechanism of the different dosage forms. The single unit CR dosage form called "tablet B" in the previous report (2) was an HPMC matrix tablet that was sensitive to the frictional force caused by the rotating basket method. Increased BG release did not occur in the rotating basket method, however the BG granules recovered from the dissolution apparatus could be easily crushed between the fingers like caviar. These differences between tablet B and BG may have caused the difference in postprandial release.

Comparing *in vitro* and *in vivo* drug release, the individual drug release rates of AG and BG in the fasted state did not exceed the *in vitro* release rate of 10 rpm of the paddle (Fig. 4). This apparently slow rate of *in vivo* drug release is in accord with previous results using single unit formulations (1). This may because of a low flow rate around dosage forms, a high viscosity of GI contents and/or a small effective surface area. Newton and his co-workers (3) showed that pellets administered orally to humans sank to the bottom of the stomach and did not move freely in the gastric fluid. This suggests that low agitation strength can also occur in the case of multiple unit formulations.

AG release in the rotating dialysis cell method without test fluid in the cell was much slower than that in the paddle method (Fig. 4). The non-sink condition in the cell might slow down AG release. A few subjects showed very a slow release rate from AG similar to that in the rotating dialysis cell method. The apparent low *in vivo* release rate may be related to a small volume of aqueous fluid in the GI tract compared with that of conventional *in vitro* dissolution tests.

In our previous studies (1,2), the mean release-time profiles of tablets in humans in the fasting state showed biphasic characteristics; in the first phase (0–4 h), A and B showed almost zero order release, and in the second phase (after 4 h), release rates decreased. The slower drug release after 4 h was assumed to correspond to drug release occurring in the colon, since by that time, the tablet would have reached the colon in humans in the fasting state (9). In the present study, drug release from granules in the colon did not seem to be reduced judging from the continuous *in vivo* release after 4–6 hr, when the granules reach the colon. The ratio of the amount released

in the colon (from 5 to 10 h) versus the total amount released in GI tract until 10 hr is shown in Fig. 5. The amount of acetaminophen released in the colon in the fasting state was significantly larger for multiple unit dosage forms than for single unit dosage forms. The reasons for the low drug release and absorption rate in the colon included the high viscosity of the luminal contents and reduced motility. Under such conditions, an increase in the effective area and the facilitation of the movement of the multiple unit formulations would improve drug release.

From this study, we conclude that the *in vivo* release of drug from a multiple unit CR product that is structurally weak is affected by mechanical stresses, which differ among human subjects but are increased by food ingestion. Also, it has been concluded that colonic release from multiple unit CR products is larger than that from single unit products. Thus, it is necessary to consider the mechanically destructive forces and colonic release to establish predictability in *in vitro* systems. None of the official methods seem to include suitable destructive forces especially for disintegration of oral CR dosage forms.

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