Oral Solid Controlled Release Dosage Forms: Role of GI-Mechanical Destructive Forces and Colonic Release in Drug Absorption Under Fasted and Fed Conditions in Humans

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Purpose. This study was undertaken to examine the effects of mechanical destructive forces on drug release from controlled release (CR) dosage forms *in vitro* and *in vivo* and their colonic release, using two CR tablets of acetaminophen A and B, showing slower and faster erosion rates, respectively. ***Methods.*** *In vitro* release rates were determined by several official methods. Tablets were administered to healthy volunteers under fasting and fed conditions. ***Results.*** Both tablets showed similar release rates under mild destructive conditions (e.g., paddle method at 10 rpm) but CR-B showed faster release under highly destructive conditions (e.g., rotating basket method at 150 rpm), where the tablet was eroded. The *in vivo* release from CR-B was faster than from CR-A, possibly because of enhanced erosion. The variable *in vivo* release from CR-B indicated large inter-subject differences in destructive GI forces. The fastest *in vivo* release from CR-B among individuals was approximated by the *in vitro* dissolution determined by destructive methods such as the rotating basket at 150 rpm. The slowest *in vivo* release from tablets A and B was lower than the dissolution by the paddle method at 10 rpm. The release from both tablets was markedly reduced at 3–4 hrs after dosing irrespective of feeding conditions which can be attributed to release inhibition in the colon. ***Conclusions.*** Effects of GI destructive forces on the tablet erosion and the release inhibition in the colon must be considered in the development of CR dosage forms.

KEY WORDS: controlled release; colonic release; drug absorption.

INTRODUCTION

For efficient development of controlled-release (CR) dosage forms, predictable *in vitro* systems should be established that reflect gastrointestinal (GI) factors affecting the dosage form performance. Among the GI factors, the effects of pH on drug release have been extensively investigated but little is known about physical factors in the GI tract such as hydrodynamic flow and mechanical destructive forces that will arise from digestive actions (grinding or crushing of GI contents) and/or friction between drug products and the GI wall. Studies on the physical factors in the GI tract are inevitable to establish *in vitro* testing systems with optimal destructive forces and hydrodynamic flow. In a previous study, we determined the GI hydrodynamic flow around dosage forms to be slow (1). Few studies focus on mechanical destructive forces (2,3). Destructive forces are especially important for CR products (4-6), because their unexpected destruction or erosion provides dose-dumping and retarded erosion results in a low drug concentration in blood.

Absorption and release of drugs in the lower intestine have important roles in extended absorption and enhanced bioavailability from CR dosage forms. Failure to achieve prolonged absorption of CR products was ascribed to poor permeability of drugs in the colon (5). However, inadequate drug release in the colon may also play a role (1,7,8).

In the present study, we first examined the GI mechanical destructive force affecting the performance of CR dosage forms and secondly, the colonic release behavior. Two experimental CR tablets of acetaminophen, A and B were employed which had been shown to erode at different rates (A: slower, B: faster) in dogs and hardly release the drug in the colon (8). *In vitro/in vivo* correlations were also examined.

MATERIALS AND METHODS

Model Tablets

Two CR tablets (8 mm in diameter) containing 100 mg of acetaminophen were prepared with 50 mg of ethylcellulose (tablet A) and 100 mg of hydroxypropylmethylcellulose (tablet B), respectively. Both preparations were generously supplied by Yamanouchi Pharmaceutical Co. (Shizuoka, Japan).

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) and second fluids (pH 6.8). Release rates were determined in 500 mL of test medium by JPXII paddle (10-150 rpm), rotating basket (10-150 rpm) and flow-through cell methods (0.9-44.5 cm/min) with a small cell of 12 mm in diameter. Release rates were also determined in 700 mL of the test fluid using the JPXII disintegration apparatus at 30 cpm without the plastic disk and at 10 cpm with or without disks. The amount of acetaminophen released in the test fluid was spectrophotometrically determined. The changes in the size of the tablets during the dissolution tests were determined after taking out the tablets from the dissolution medium followed by drying in cold air blow.

In Vivo Test

Seven healthy volunteers (two women and four males) ranging from 25 to 52 years of age participated in the study with written informed consent. A test tablet was administered to subjects together with 200 mL of water after fasting overnight or immediately (within 5 min) after intake of 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 appropriate times for up to 24 hrs and stored at −20 °C until assay. Test tablets were administered with at least a 1-week interval according to a cross-over design. On the other hand, all subjects were orally administered 100 mg acetaminophen solution after fasting overnight

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Table I. Amount (%) of Acetaminophen Released in 8 hrs from Two CR Tablets A and B by Different *in Vitro* Methods

			Tablet	
		Remarks[a]	A	B
Paddle	10 rpm		60	57
	10 rpm	Surfactant[b]	58	60
	10 rpm	pH 4.0	60	61
	10 rpm	pH 1.2	59	61
	50 rpm		64	64
	100 rpm		68	91
	150 rpm		72	94
Rotating basket	10 rpm		61	64
	50 rpm		67	77
	100 rpm		69	85
	150 rpm		69	91
Flow-through cell	0.9 cm/min		60	58
	14.9 cm/min		58	65
	44.5 cm/min		67	72
Disintegration	10 cpm		69	90
	10 cpm	with disks	97	98
	30 cpm		93	96

[a] pH 6.8 buffer was used unless described specifically.
[b] 0.2% polysorbate 80 in pH 6.8 buffer.

and saliva samples were collected. The concentrations of acetaminophen in saliva were determined by high-performance liquid chromatography as previously reported (1).

Bioavailability was estimated using the concentrations of acetaminophen in saliva which have been reported to be proportional and virtually equivalent to the blood concentrations (9). The maximum drug concentration in saliva (C_{max}) and time to Cmax (T_{max}) were the observed values. The area under the drug concentration-time curve from zero to 10 hrs (AUC_{10hr}) was calculated by means of a trapezoidal rule. Mean residence time (MRT) was determined using saliva concentration data up to 10 hrs. The *in vivo* drug release from tablets was calculated by the constrained deconvolution method of Verotta et al (10), in which the oral solution data were used for weight function. The weight function was determined by using the pharmacokinetic model parameters after fitting the saliva data to a suitable compartmental model using a MULTI program (11), in which Akaike's information criterion was used for model selection.

RESULTS

In Vitro Release

The release rates from tablets A and B were expressed as the amount of drug released in 8 hrs (Table I). Fig. 1 shows the release profiles of the two tablets determined by three representative *in vitro* methods with different destructive forces. There were only small differences in the release rate between the two products when determined under mildly destructive conditions of the paddle method at 10-50 rpm, rotating basket at 10 rpm and flow-through cell method at 0.9-44.5 cm/min (Table I). Typical release profiles of both tablets were shown in Fig. 1a which were determined by the paddle method at 10 rpm. Under this mild destructive condition, tablet B became swollen and formed a transparent ghost-layer that increased as the drug was released out of the tablet as shown in Fig. 2a.

However, under the highly destructive conditions of the paddle method at 100-150 rpm, the rotating basket at 50-150 rpm and the disintegration method at 10 cpm without the plastic disk, tablet B was eroded although tablet A was not. The erosion of CR-B appeared to be caused by friction between the tablet and rotating basket or by tapping of the tablet at the wall of vessel in the paddle method where the swollen tablet moved around the test medium. The erosion observed in the rotating basket at 150 rpm and 50 rpm was shown in Fig. 2b and Table II. As a result of the erosion, CR-B showed faster release than CR-A. Their typical release profiles determined by the rotating basket at 150 rpm were shown in Fig. 1b.

Under the very highly destructive conditions of the disintegration method at 10 cpm with the plastic disk and at 30 cpm without disks, both products were eroded and gave similarly fast releases (Table I). The erosion seemed to be brought about by striking of tablets against the plastic disk and/or bottom of the cylindrical tube of disintegration apparatus. Their release profiles and erosion determined by the disintegration method at 30 cpm without disks were shown in Figs. 1c and 2c.

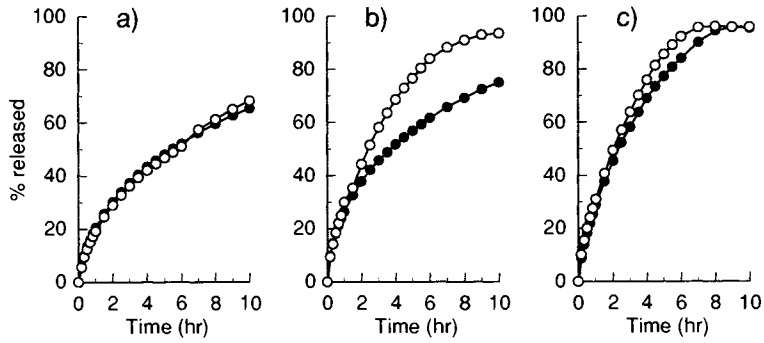

Fig. 1. In vitro release profiles of acetaminophen from tablets A (●) and B (○) determined by a) the paddle method at 10 rpm, b) rotating basket method at 150 rpm and c) disintegration method at 30 cpm. The data are the means of three independent measurements.

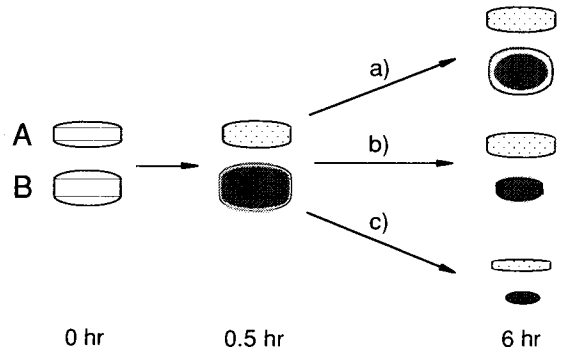

Fig. 2. Changes in shape of tablets A and B observed during *in vitro* dissolution determined by a) the paddle method at 10 rpm, b) rotating basket method at 150 rpm and c) disintegration method at 30 cpm, having low, high and very high destructive conditions.

In Vivo Release

Table III shows the mean pharmacokinetic parameters of tablets A and B in humans under fasting and nonfasting conditions. The mean relative availability (F_{rel}) from CR-B was significantly higher than that from CR-A under either fasting or fed condition. Food did not significantly affect their bioavailabilities.

Fig. 3 shows the mean *in vivo* release profiles of acetaminophen. Statistically significant differences were found in the amount released in 10 hrs between tablets A and B under fasting and fed conditions. Food did not significantly affect the mean releases from either tablet. However, individual releases shown in Fig. 4 suggested that food promoted the *in vivo* release in some subjects and inhibited it in others, which was notable for CR-A. The increase might be caused by the enhanced GI destructive forces due to food (12,13) and the decrease by the effect of high viscosity and/or adsorption of fat components in the diet on the tablet (14) as observed in dogs (15). Food also caused a lag phase in the drug release in several subjects, which seemed to be brought about by the inhibitory effects of food on gastric emptying (16).

Release profiles in most individuals exhibited a biphasic pattern irrespective of feeding conditions, rapid release up to 3 or 4 hrs followed by very slow releases (Fig. 4). Judging from the colonic arrival time for single unit dosage forms to be around 4 and 6 hrs under fasting and nonfasting conditions (16), the slow releases in the later phase correspond to the dissolution in the lower intestine including the colon.

Compared with CR-A, CR-B showed a faster release in many subjects under both fasting and nonfasting conditions, which can be attributed to the accelerated erosion caused by GI destructive forces, judging from the erosion-dependent release characteristics (Figs. 1 and 2) and its actual erosion in dogs (8,15). The large inter-subject differences in dissolution from CR-B indicate differences in GI destructive forces among subjects. GI destructive forces seem smaller in the lower intestine compared with the upper GI tract (6), which correlates with the very slow release after 4 hrs (Fig. 4).

In Vitro - In Vivo Correlation

When the dissolution from dosage forms is significantly affected by physiological variables such as pH and mechanical stress, it is difficult to correlate the entire *in vivo* release profile with the *in vitro* profile determined only by a single method at a fixed pH and stirring rate (17), because the *in vivo* release will change depending on GI pH and flow rate which vary with the GI site, time, and individual. For such environment-dependent processes, usual correlation studies that relate a single *in vitro* release profile with average *in vivo* profiles alone may not be appropriate. It is important to know the variable range of their *in vivo* release between or within subjects which is achievable by establishing an *in vitro/in vivo* correlation for upper and lower limits of *in vivo* releases, but no attempts have been made until now. Such a correlation study will be particularly important for CR products that aim to keep the drug concentration within a therapeutic range.

Therefore, correlations were assessed for the fastest and slowest *in vivo* releases among individuals (Fig. 4). The fastest *in vivo* release of CR-B under fasting and fed conditions was similar to the *in vitro* curve determined by the rotating basket method at 150 rpm or disintegration method at 10 cpm without the disks (data not shown). The slowest release from CR-B until 3 hrs under a fasting condition was less than the *in vitro* dissolution curve by the paddle method at 10 rpm. Most *in vivo* releases from CR-A under a fasting condition were slower than the *in vitro* release by the paddle method.

The slowest *in vivo* releases under a fed condition of both tablets were much slower than the dissolution curve by the paddle method, that is ascribable to the inhibitory effects of food on their *in vivo* dissolution as stated above.

DISCUSSION

Studies using various dosage forms with different characteristics have resulted in unpredictable correlations between *in vitro* and *in vivo* data. Some investigators found a good correlation by using the rotating basket (18,19) or flask methods (19) and others using the paddle method (20). Dissolution is affected by two main physical factors, hydrodynamic flow and mechanical destructive forces. Better *in vitro/in vivo* correlations for destructive *in vitro* methods such as disintegration (21) and rotating basket methods (19) than for the paddle or beaker methods with low destructive forces suggested significant effects of GI destructive forces.

Table II. Change in Size of Tablets A and B During Dissolution by Rotating Basket Method at 50 rpm

Tablet	Time (h)	Diameter[a] (mm)	Thickness[a] (mm)
A	0	8.0	3.6
	2	8.2	3.6
	4	8.1	3.6
	6	8.1	3.6
	10	8.1	3.6
B	0	8.0	4.6
	2	8.4	4.7
	4	6.8	3.7
	6	5.5	2.9
	10	n.m	n.m

[a] Values given are average of two measurements. n.m: not measurable due to formation of lump.

Table III. Pharmacokinetic Parameters of Acetaminophen (mean ± SD, $n = 7$) After Administration of Two CR Tablets (100 mg) to Humans Under Fasting and Fed Conditions

	Tablet			
	A		B	
	Fasting	Fed	Fasting	Fed
$AUC_{10\ hr}$ (ng/ml · h)	2588 ± 1426	2207 ± 1060[b]	3903 ± 2175	3509 ± 1726[b]
Frel[a]	0.44 ± 0.18[b]	0.40 ± 0.06[b]	0.68 ± 0.09[b]	0.63 ± 0.09[b]
Cmax (ng/ml)	503 ± 251	394 ± 151[b]	717 ± 336	714 ± 377[b]
Tmax (h)	3.04 ± 1.76	3.29 ± 0.76	2.45 ± 1.56	3.86 ± 1.21
MRT (h)	4.27 ± 0.28	4.61 ± 0.50	4.42 ± 0.57	4.49 ± 0.57

[a] Frel: relative bioavailability calculated using solution data ($AUC_{10\ hr}$: 5497 ± 1214 ng/ml · h).
[b] Significant difference ($p < 0.05$) between tablets A and B.

To establish predictable *in vitro* systems, the two physical factors must be clarified and compared among *in vitro* testing systems. In this study, we examined GI mechanical destructive forces, using two CR tablets of acetaminophen, A and B having different sensitivity to mechanical stress. Their colonic release behavior was also examined.

In vivo releases of both tablets under fasting and fed conditions were markedly decreased when the tablets reached the colon (Fig. 4). This decrease can be attributed to release inhibition in the lower intestine but not to poor permeability of acetaminophen in that region, because both CR tablets were already proven to release hardly any drug in the colon of dogs (8). Further, the colonic absorption rate (23 % in 10 min) of acetaminophen (22) is faster than the release rates from tablets A and B, even though the colonic absorption rate is two to three times slower than that in the small intestine. Third, Another study using dogs (23) showed that acetaminophen was absorbed from the colon to a similar extent as from the small intestine if drug release was not limited in the colon. The low release in the colon is ascribable to the small volume of GI fluid, viscous colonic contents and decreased intestinal motility which restrict fluid movement around dosage forms and retard dissolution, especially of poorly soluble drugs. In addition, the decreased motility of the colon delays the erosion of drug products and hence dissolution. Therefore, we must consider not only the colonic permeability of drugs but also the colonic release characteristics of CR products. *In vitro* testing systems to predict the colonic release behavior will be required.

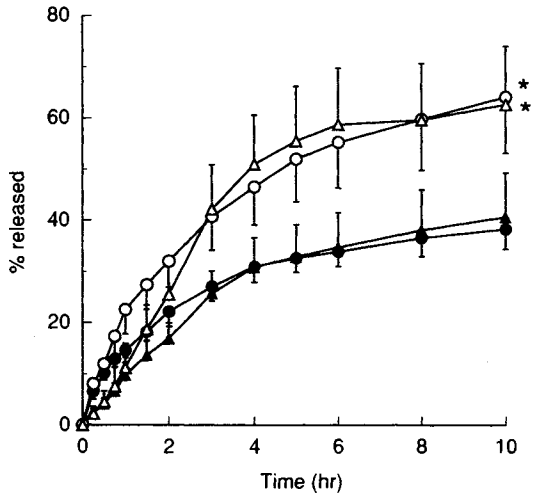

Fig. 3. *In vivo* release profiles of acetaminophen in humans after administration of tablets A (closed symbol) and B (open symbol) under fasting (circle) and fed conditions (triangle). Each points shows the mean of seven subjects with SE. * significant difference ($p < 0.05$) between two tablets.

The faster release from tablet B than from A in most subjects (Fig. 4) can be attributed to enhanced erosion as a result of GI destructive forces, because 1) tablet B showed erosion-dependent release which is not influenced by pH or sufactants, 2) tablet B was more strongly eroded than tablet A under a highly destructive condition (Fig. 2b) and released the drug faster *in vitro* (Fig. 1b), 3) previous study of dogs (8,15) showed that tablet B also gave a faster *in vivo* release than A, especially under fed conditions (15), where the tablet B recovered from the GI tract was more eroded than tablet A, particularly under fed conditions, and 4) erosion-dependent dissolution in humans was reported for a hydroxypropylmethylcellulose-matrix tablet (6) which was similar in formulation to tablet B.

Large inter-subject differences in drug release observed for the erodable tablet B (Fig. 4) may be caused by differences in GI destructive force among subjects. A significant correlation ($r = 0.789$, $p < 0.05$) was observed in the amounts dissolved from CR-B in 10 hrs in individuals between fasting and nonfasting states. This suggests that GI mechanical destructive forces differ with the human subject. The fastest *in vivo* release was approximated by the dissolution curves determined under highly destructive conditions such as by the rotating basket at 150 rpm. Therefore, the *in vitro* testing condition shown in Fig. 2b is similar to the maximum GI destructive condition. However, even more destructive conditions such as the disintegration method at 30 cpm shown in Fig. 2c are considered non-physiological, judging from the very fast *in vitro* release from CR-A that was not comparable to the *in vivo* release.

On the other hand, the slowest release of tablets A and B under fasting conditions was less than the dissolution determined under the very mild destructive conditions of the paddle method at 10 rpm (Fig. 4). Thus, the minimum GI destructive condition is less than that of the paddle method shown in Fig. 2a, where tablet erosion was limited. Under

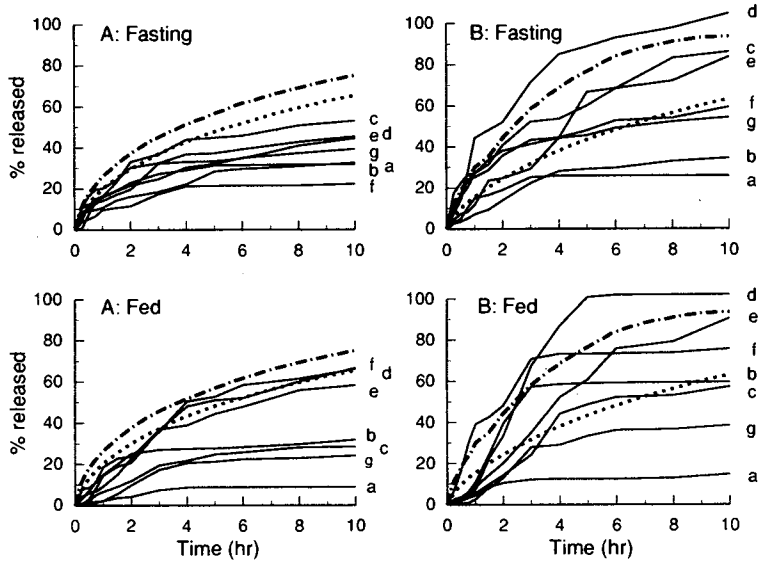

Fig. 4. *In vivo* release profiles (——) of acetaminophen from two CR tablets, A and B in individual subjects a–g under fasting and fed conditions and *in vitro* releases determined by the paddle method at 10 rpm (----) and rotating basket method at 150 rpm (---).

such a condition, the drug will be released depending only on GI hydrodynamic flow, indicating that the flow rate around dosage forms is slow as suggested by previous studies (20). This low flow rate may result from a higher viscosity of GI fluids than that of *in vitro* test fluids and/or limited surface area of tablets for dissolution because of smaller volume of GI fluids.

The correlation results indicate that the low and high *in vitro* destructive conditions shown in Fig. 2a and 2b are physiologically meaningful but not the very high destructive condition shown in Fig. 2c. The variable range of GI destructive conditions should be defined by further studies using other dosage forms and reflected on *in vitro* systems, by which the variability in dissolution caused by GI destructive forces will be predictable.

In conclusion, it is necessary to consider the effects of mechanical destructive forces on drug releases that differ with the subject and the release behavior in the lower intestine for the development of CR dosage forms.

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