Estimation of Agitation Intensity in the GI Tract in Humans and Dogs Based on *in Vitro/in Vivo* Correlation

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In this study, we assessed the hydrodynamic flow around a dosage form in the GI tract in humans by comparing the characteristics of *in vitro* and *in vivo* release of two different types of controlled release acetaminophen (paracetamol) tablets, A and B. The former tablet showed an agitation speed-dependent release at a high speed range (50–100 rpm), whereas the latter showed this characteristic at a low speed range (10–50 rpm). The mean release amount-time profiles of tablets A and B in humans showed biphasic characteristics, and the first phase of the absorption profiles of A and B was close to their *in vitro* profiles at a paddle speed of 10 rpm. The *in vivo* profiles were also superimposable on *in vitro* dissolution curves obtained by the flow-through cell method at a flow rate of 1 mL/min (velocity 0.89 cm/min) or less. These results indicate that the hydrodynamic flow around the dosage forms in the human GI tract could be extremely low. The *in vivo* release rate of these tablets in dogs was greater than in humans, and was estimated to be equivalent to the release rate determined by the paddle method at 100 rpm. This indicates that a higher agitation intensity in the GI tract in dogs than in humans may be one cause of the discrepancies between humans and dogs in drug absorption studies.

KEY WORDS: absorption; dissolution tests; hydrodynamic flow in GI tract; controlled release; *in vitro/in vivo* relationship; acetaminophen.

INTRODUCTION

The development and evaluation of a formulation is facilitated if *in vitro* testing can predict *in vivo* performances. To establish a useful *in vitro* dissolution testing system for oral dosage forms, it is important to understand the fate of an administered dosage form, and in particular, the gastrointestinal (GI) factors affecting drug release. The major GI factors affecting dissolution properties include: pH, viscosity, and concentration of surfactant. The effects of GI fluid characteristics, especially pH, on dissolution have been extensively investigated. However, the effects of physical factors such as the hydrodynamic flow of GI fluid and the mechanical destructive forces due to GI motility on *in vivo* dissolution are poorly understood.

The present study was undertaken to clarify GI hydrodynamic conditions surrounding dosage forms, based on an *in vitro/in vivo* comparison of drug release properties. We prepared two different types of controlled release acetaminophen (paracetamol) tablets, both of which showed agitation speed-dependent release, one at a low speed range (10–50 rpm), and the other at a high speed range (50–100 rpm). According to previous results, we anticipated that these ranges would cover the agitation intensity in the human GI tract (1–5). The animal studies were carried out to reveal differences in GI agitation intensity between humans and dogs, since our previous studies (6) suggested that GI motility in dogs was stronger than in humans, possibly accounting for greater bioavailability in dogs of products with poor availability in humans.

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MATERIALS AND METHODS

Dosage forms

Two types of controlled release tablets (8 mm diameter, 3 mm thick) of acetaminophen were prepared by direct compression. The components of the tablets are shown in Table I. The drug release rates were controlled by the dissolution characteristics of the components fumarate and tryptophan. The correct ratio of acidic (fumarate) and basic (tryptophan) excipients makes dissolution of the tablets independent of pH, and the side wall of the tablets was coated with ethylcellulose so that the dissolution properties were near zero order release, as previously reported (7). Acetaminophen (p-hydroxyacetanilide) and o-hydroxyacetanilide (internal standard for HPLC) were purchased from Tokyo Chemical Industry Co. Ltd. (Japan). All other reagents used were of analytical grade and available from commercial suppliers.

In vitro drug release

Dissolution tests were carried out at 37°C with 900–2000 mL of dissolution media, using the JP XII paddle, JP XII rotating basket (rotating speed fixed at 50 rpm), and USP flow-through cell (cell diameter 12 mm) methods. The rotating dialysis cell method (8) was also used, in which 5 mL of medium was placed in a cell made with HVLP (Millipore® membrane) set at 15 hrpm horizontal rotation in 900 mL of dissolution medium at 37°C. For all dissolution tests, except for the study of pH effect, JP XII 2nd fluid (pH 6.8, for disintegration test) was used. The effects of pH and polysorbate 80 (0.01%) on drug release were investigated by the paddle method. The amount of drug dissolved was determined by the HPLC method described below, in which the sample solution was filtered and directly injected. All tests were carried out in duplicate or triplicate.

In vivo studies

Human Study

In the human study, the drug release amount and bioavailability parameters were calculated using the saliva concentration of acetaminophen; this has been reported to be proportional and virtually equivalent to serum drug concentration (9). Six healthy volunteers, five males and a female (age range, 30 to 52 years; weight, 50 to 67 kg) participated in the study after giving their written informed consent. The volunteers received a test tablet together with 200 mL of water in a crossover fashion according to a randomized

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Table I. Composition of Controlled Release Acetaminophen Tablets

Component (mg)	A	B
Acetaminophen	100.0	100.0
Fumarate	71.4	72.0
dl-Tryptophan	24.0	24.0
Corn starch	2.6	—
Magnesium stearate	2.0	—
Hydroxypropylcellulose	—	4.0
Total	200.0	200.0

block design. They were also given 100 mL of solution containing 100 mg of acetaminophen together with 100 mL of water, and there was at least a 7-day washout period between dosing. The volunteers were fasted from 10 h before to 4 h after the drug administration. Saliva samples were collected spontaneously for by each volunteer 1 to 2 min into a centrifuged tube for up to 24 h after dosing. The samples were frozen at −20 °C until analyzed.

Dog Study

Six male beagle dogs, weighing 12.0–15.5 kg, received a test tablet together with 30 mL of water in a crossover fashion according to a randomized block design, followed by i.v. and p.o. solution administration studies with a 7-day washout period between each dosing. The dogs were fasted for 12 h prior to and for 8 h after receiving the products. They were also given a 100-mg dose of acetaminophen solution orally and 50 mg of acetaminophen intravenously. Blood samples (3-mL) were taken for up to 24 h, and the plasma samples were kept frozen at −20 °C until assayed.

Analytical Methods

Acetaminophen was determined by high performance liquid chromatography at 240 nm using a column of Inertsil ODS-2 (150 × 4 mm, GL Science Inc., Japan) at 50 °C. The eluents used were: A, 1.5% acetic acid containing 15% methanol (for plasma sample); B, methanol-acetonitrile-0.05 M phosphate potassium buffer (pH 2.5) (8:7:85) mixture (for saliva and dissolution samples) at a flow rate of 1 mL/min.

Prior to analysis, the frozen samples were thawed out at room temperature and centrifuged at 3000 rpm for 20 min after vigorous mixing to remove precipitants of protein. To a 500-μL aliquot of saliva or plasma, 100 μL of 100 μg/mL o-hydroxyacetanilide internal standard solution and 5 mL of ethylacetate were added. The mixture was shaken for 15 min and then centrifuged at 2500 rpm for 5 min. A 4-mL aliquot of the supernatant was taken and dried under a stream of nitrogen at 50 °C. The residue was reconstituted with 200 μL of eluent, and a 50-μL volume was injected onto the column. Retention times of acetaminophen and o-hydroxyacetanilide were 4.7 and 9.9 min, respectively, for eluent A, and 4.0 and 8.0 min for eluent B. The average recovery value for acetaminophen was 94.3% from plasma and 103.3% from saliva. The coefficients of variation of acetaminophen analysis varied from 0.5 to 5.3% over the range 1.0 to 50.0 μg/mL of acetaminophen, and the correlation coefficient of the standard curve was 0.999. The quantification limit for acetaminophen was about 100 ng/mL (CV 10%).

Data Analysis

Drug absorption in the dog following oral administration was calculated by point-area deconvolution (10) using i.v. administration data for weight function. When the i.v. data were used for weight function, the cumulative absorbed amount was normalized for the relative bioavailability of the p.o. solution to correct the first-pass metabolism effect in individual dogs. Because of the very fast absorption rate of acetaminophen from oral solution, the drug release profile from the slow release dosage form seemed to be reasonably reflected in the normalized absorption profile in the dog. The drug release in humans following oral administration was calculated by the constrained deconvolution method of Verotta et al (11), in which p.o. solution data were used for weight function. The weight function of deconvolution was determined by using the pharmacokinetic model parameters in all cases; these were fitted to a compartment model using the MULTI (12) program, in which Akaike's information criterion was used for model selection.

RESULTS

***In vitro* dissolution test**

The drug dissolution rate from tablet A was virtually unaffected by the agitation intensity at the range of 10–50 rpm paddle speed; however, it was slightly accelerated at 100 rpm (Fig. 1-A1). In contrast the dissolution rate of tablet B was greatly affected by agitation intensity at the range of 10–50 rpm paddle speed (Fig. 1-B1). The drug dissolution rate determined by the rotating dialysis cell method at 15 hrpm cell rotation was similar to that by the paddle method at 100 rpm for B, whereas, with A, the former exceeded the latter. The following observations suggested that A is more sensitive to destructive force: In the rotating dialysis cell method, the tablet is rolled in the membrane cell, and is gradually eroded from the surface due to friction between the tablet and membrane, which promotes dissolution. In contrast, in the paddle method, the tablet stays on the bottom of the dissolution apparatus without movement when the paddle speed is less than 100 rpm. The difference in dissolution rates between A and B could be due to differences in hydrophilicity between recipients. The difference in sensitivities for erosion between A and B could reflect the relationship between spontaneous dissolution rate (dissolution without destructive force) versus surface destruction rate. The two types of tablets tested did not disintegrate; however, the surface of the tablets would be gradually destroyed if there was a mechanical stress. If the spontaneous dissolution rate is large, as for B, destructive forces contribute little to promote drug release, whereas if the spontaneous dissolution rate of a tablet is relatively small, as for A, destructive forces contribute greatly to promote drug release.

In the flow-through cell method, the drug dissolution rates increased with increases in the flow rate of the dissolution medium (Fig. 1-A2, B2), although there was no difference in dissolution rates at flow rates of 1 and 2 mL/min (velocity of 0.89 and 1.76 cm/min). In the rotating basket

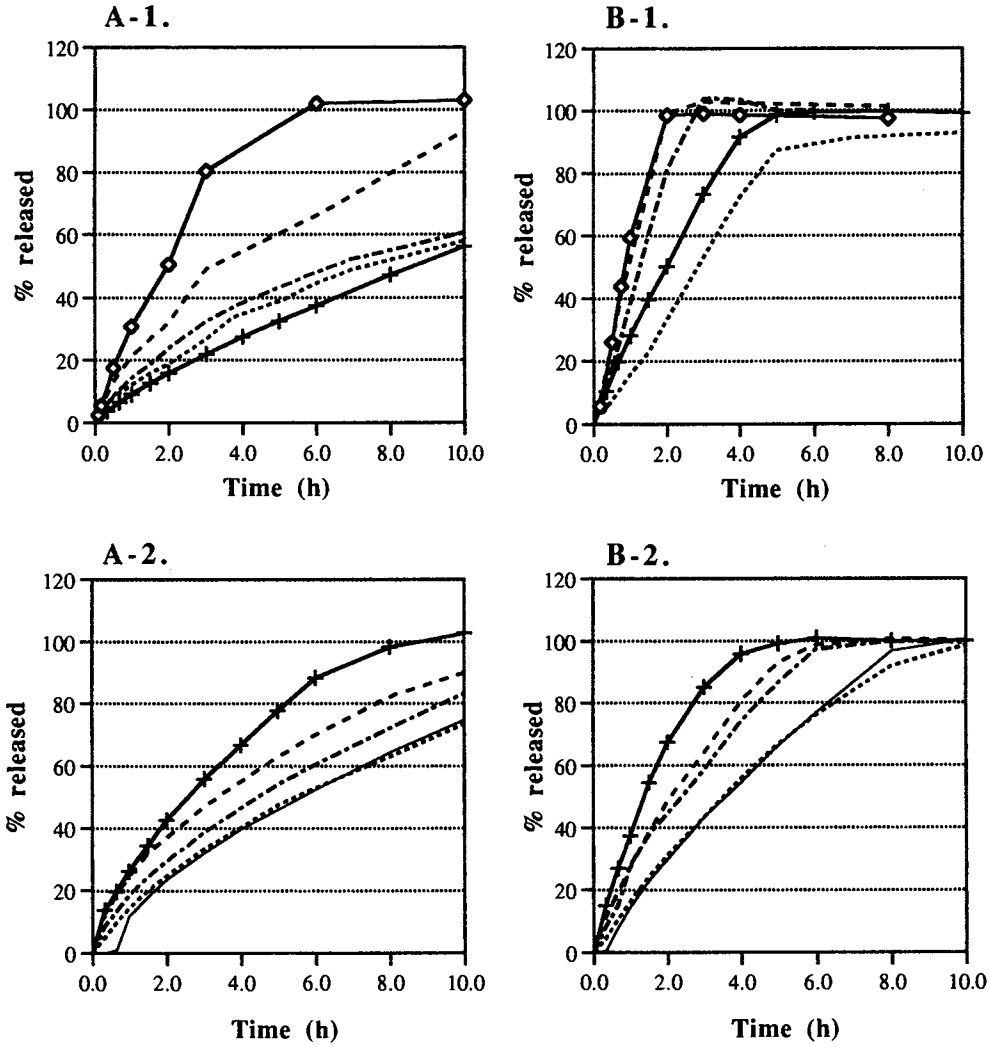

Fig. 1 *In vitro* amount of acetaminophen released from controlled release tablets A and B by four different test methods A-1. *In vitro* mean release profiles of tablet A by paddle method at 10 rpm (·····), 50 rpm (–·–·–), and 100 rpm (– – –); by rotating dialysis cell method at 15 hrpm (–◇–); and by rotating basket method at 50 rpm (–+–). A-2. *In vitro* release profile of tablet A by flow-through cell method at 1 mL/min (——), 2 mL/min (·····), 8.3 mL/min (–·–·–), 16.7 mL/min (– – –), and 50 mL/min (–+–). B-1. *In vitro* release profiles of tablet B. Symbols are the same as in A-1. B-2. *In vitro* release profiles of tablet B. Symbols are the same as in A-2.

method, although the drug dissolution rates were near those of the paddle method at 10 rpm, this method showed the largest difference between A and B of all the dissolution test methods used.

The drug dissolution from both types of tablets was virtually unaffected by the addition of polysorbate 80 and by changes in pH (data not shown). The CV of dissolution data at each sampling point ranged from 2 to 5% for the paddle method at 10 rpm, the flow-through cell method at 50 mL/min, and the rotating dialysis cell method. At other rotation speeds and flow rates, all the CV were less than 2%.

In vivo drug release

The mean drug levels in human saliva and dog plasma after the oral administration of tablets A and B are shown in Fig. 2, and the model-independent parameters are shown in Table II. In all cases, the C_{max} and AUC for B were larger than those for A; however, there was no significant ($p < 0.05$) difference in pharmacokinetic parameters between A and B. The mean release amount-time profiles of tablets A and B in humans showed biphasic characteristics (Fig. 3); in the first phase (0–4 h), A and B showed almost zero order release, and in the second phase (4 h-), the release rates decreased. The slower drug release after 4 h was assumed to correspond to the release in the colon, since by that time, the tablet would have reached the colon in humans (13). The decreased drug absorption in the colon probably reflected decreases in water content and in the GI motility in the colon, not a decrease of the intrinsic absorption rate. The reported absorption rate of acetaminophen in the colon (14) was considered to be much faster than the release rate, although the colonic absorption rate is two to three times slower than that in the small intestine.

Upon comparing the *in vitro* and *in vivo* profiles, we

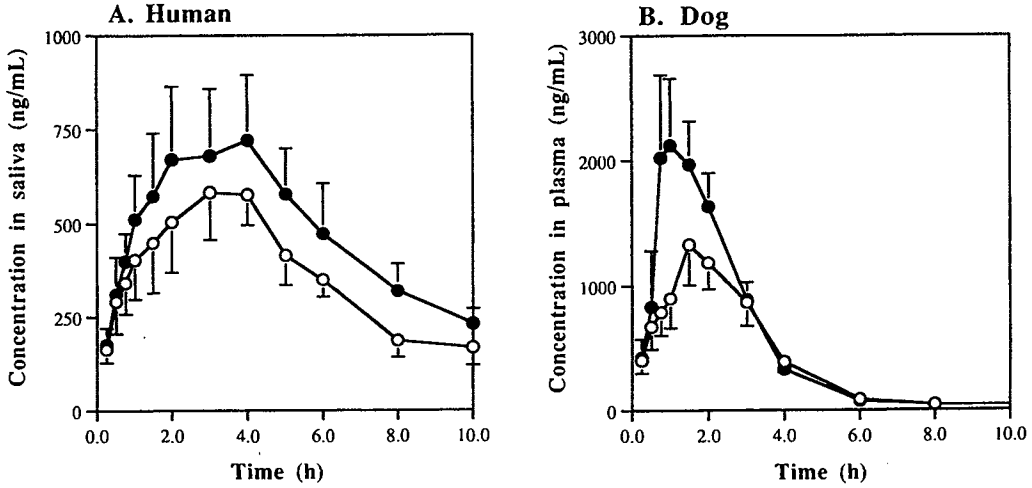

Fig. 2 Mean (n = 6) acetaminophen concentration in human saliva and dog plasma after administration of controlled release tablets A (○) and B (●). Vertical lines show SE.

found that the absorption profiles of A and B in the first 1–2 h were close to the *in vitro* profiles at 10 rpm paddle speed (Fig. 3). These absorption profiles of A and B were also superimposable on the *in vitro* dissolution curves obtained by the flow-through cell method at a flow rate of 1–2 mL/min (velocity, 0.89–1.79 cm/min). The *in vivo* release profiles of B after 2 h differed from the *in vitro* release profiles in the paddle method at 10 rpm, although they were close to the profile obtained by the flow-through cell method at 1 or 2 mL/min (Fig. 3). When the flow rate in the flow-through cell method is very low, sink condition is hardly kept up. These appear to be close to the condition of the GI tract, in which sufficient fluid dissolving the drug was possibly not supplied, unlike the paddle method, in other words, a sink condition was unlikely to exist in the GI tract. The *in vivo* release rate of A was higher than that determined at 10 rpm paddle speed. As described above, A was more sensitive to destructive force than B. Thus, destructive force may have elevated the apparent flow rate for A *in vivo*. The observed *in vivo* hydrodynamic flow rates naturally include mechanical destructive force due to GI motility, hence, the net *in vivo* hydrodynamic flow could be less than that achieved at 10 rpm paddle speed.

In the beagle dog, the *in vivo* release rate of tablet B was almost equal to the *in vitro* release rate at 100 rpm by the paddle method (Fig. 4) and was far greater than that in humans. This vigorous GI condition in the dog may be responsible for the discrepancies between humans and dogs in drug absorption studies (1,6,15). In the flow-through cell method, the highest flow rate, 50 mL/min (45 cm/min velocity, this flow rate being maximum for our apparatus), did not reach the drug release rate in dogs (Fig. 4). Such a high flow rate is unlikely to reflect actual GI fluid flow. The destructive force in the GI tract could largely contribute to the promotion of drug release in dogs. This consideration was supported by the result that dissolution in the rotating dialysis cell method was most similar to the *in vivo* release profiles in the dog, especially for A (Fig. 4).

Table II. Pharmacokinetic Parameters of Acetaminophen (mean ± SD, n = 6)

		Oral dosage form[b]		
	i.v. (50 mg)[a]	Solution (100 mg)	A	B
Human				
AUC_t, ng/mL · h	—	6419.2 ± 2355.4	4824.1 ± 1866.2	5968.1 ± 2506.7
F_{rel}, %	—	100.0	75.4 ± 19.9	91.0 ± 14.9
C_{max}, ng/mL	—	4267.2 ± 2866.5	622.7 ± 294.5	690.3 ± 377.5
T_{max}, h	—	0.19 ± 0.13	3.33 ± 0.82	3.83 ± 1.17
MRT, h	—	3.25 ± 0.24	6.83 ± 2.14	7.08 ± 0.83
Dog				
AUC_t, ng/mL • h	3949.1 ± 517.9	6614.1 ± 1419.8	4509.5 ± 1127.4	5910.1 ± 1902.1
F_{rel}, %	—	100.0	70.1 ± 13.6	82.3 ± 18.6
C_{max}, ng/mL	4957.4 ± 852.0	5200.9 ± 931.4	1564.3 ± 664.8	3095.1 ± 1481.7
T_{max}, h	—	0.31 ± 0.07	1.90 ± 0.65	1.35 ± 0.49
MRT, h	0.75 ± 0.12	1.22 ± 0.09	3.51 ± 1.14	2.70 ± 0.37

AUC_t: area under the plasma concentration-time curves from zero to last sampling time, F_{rel}: relative bioavailability for solution data, C_{max}: maximum observed saliva or plasma concentration, T_{max}: time to reach the peak concentration, MRT: mean residence time.

[a] Parameters for i.v. administration data were determined by using compartment model theory following curve fittings.

[b] Parameters for p.o. administration data were determined directly from raw data.

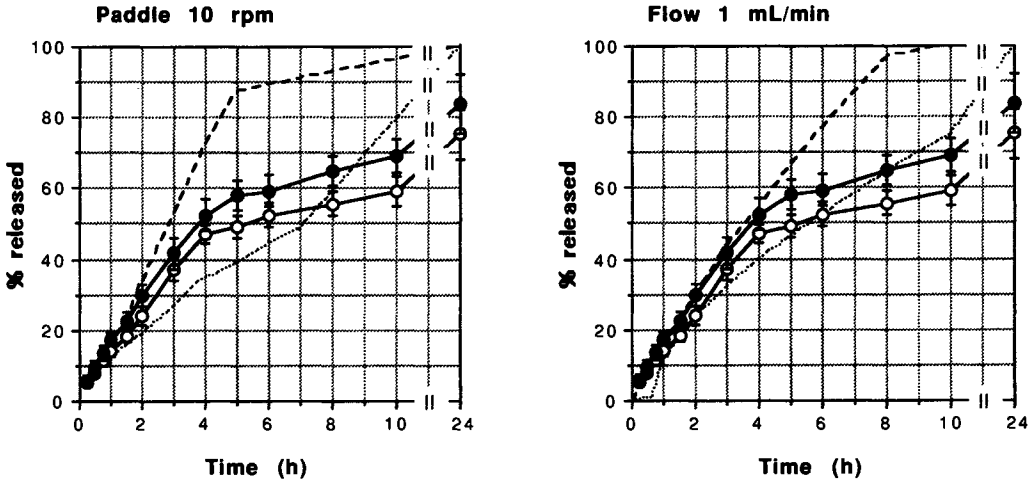

Fig. 3 Comparison of *in vitro* and *in vivo* amounts of acetaminophen released from controlled release tablets in humans. Vertical lines show SE. Key: *in vivo* ○:A, ●:B; *in vitro* ·····:A, ———:B.

DISCUSSION

The results of this study suggested that the agitation intensity in the GI tract in the dog was greater than that in humans, and the hydrodynamic flow around a dosage form in the human stomach and small intestine was much lower than expected from the *in vitro* hydrodynamic conditions created by the strength of officially specified agitation, namely, the paddle method, at 50–100 rpm rotating speed, and the flow-through cell method, at 8–15 mL/min flow rate. The present findings regarding GI fluid flow in humans are similar to the results of Dietrich et al (2), who reported that the *in vivo* release rate of controlled release theophylline pellets was slower than that of the *in vitro* release, in which the agreement between the *in vitro* and *in vivo* release rates occurred when the dissolution process was greatly slowed down. Similarly in the flow-through cell method, the extremely low flow rate resembled the *in vivo* condition, in which a sink condition was unlikely to exist.

Levy et al. (3) reported that the *in vivo* dissolution of aspirin correlated well with the *in vitro* dissolution determined by a beaker method at 50 rpm, but that there was no correlation at higher or lower rotating speeds. Hussein (4) showed that the rotating basket method at 100 rpm provided the best *in vitro/in vivo* correlation for theophylline controlled release products. Nicklasson (5) established an *in vitro/in vivo* correlation for remoxipride microcapsules, using the flow-through cell method at a flow rate of 16 mL/min, in a 12 mm diameter cell. Our previous study of indomethacin capsules provided the best *in vitro/in vivo* correlation at 30 rpm by the JP XII paddle method (1). These divergent results may reflect the different characteristics of these dosage forms.

In ordinary dissolution test methods, such as the paddle or flow-through cell methods, conditions of high hydrodynamic flow and small mechanical destructive force are present, whereas, in the GI tract, the formulation may be subjected to conditions of low hydrodynamic flow and large destructive force (Fig. 5). Several studies have suggested that the destructive forces promoted the *in vivo* disintegration of some products and, hence, their dissolution (16,17). Additionally, the destructive force in the GI tract seems to be stronger in the fed state than in the fasting state (17,18), possibly because of foodeffects. Drewe et al (19,20) studied the *in vitro/in vivo* correlation for a modified release formulation of bromocriptine based on a swelling hydrocolloid

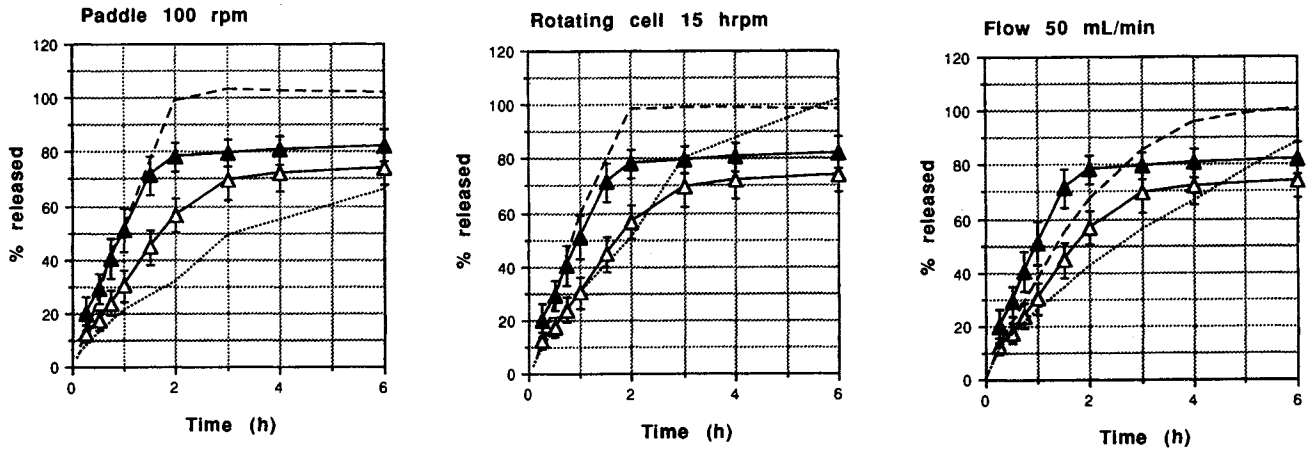

Fig. 4 Comparison of *in vitro* and *in vivo* amounts of acetaminophen released from controlled release tablets in dogs. Vertical lines show SE. Key: *in vivo* △:A, ▲:B; *in vitro* ·····:A, ———:B.

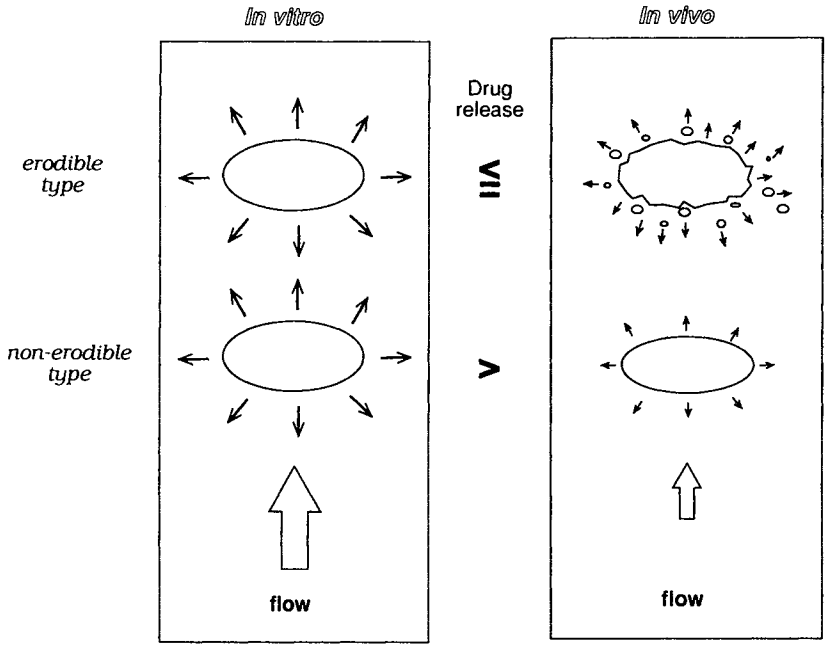

Fig. 5 Schematic representation of *in vitro* and *in vivo* drug release from dosage forms with different sensitivity to erosion.

principle, and suggested that the discrepancies between *in vitro* and *in vivo* drug release (absorption) could be due mainly to mechanical agitation and the local environment of the GI tract. Ultimately, in previous studies of *in vitro/in vivo* correlation, if a formulation was sensitive to erosion (erodible or disintegrated type formulation), the *in vivo* release rate was underestimated by *in vitro* dissolution tests under routine dissolution conditions (3,19,16,21). In contrast, if a formulation was insensitive to erosion (non-erodible type formulation coated with insoluble polymer or made with insoluble matrix), the *in vivo* release rate was overestimated (2,3,22,23). Therefore, sometimes, similarity of drug release rate the *in vitro* to the *in vivo* release rate can be obtained by performing the *in vitro* test at a higher flow rate, as a substitute for the *in vivo* mechanical stress (Fig. 5).

CONCLUSION

We have pointed out three important facts; first, the observed hydrodynamic flow rate in the human GI tract was very low, corresponding to a paddle speed of 10 rpm in the paddle method or a velocity of about 1 cm/min (1–2 mL/min flow rate) in the flow-through cell method. Second, the agitation force in the GI tract in dogs was greater than that in humans, corresponding to a paddle speed of 100 rpm or a velocity exceeding 45 cm/min (50 mL/min flow rate). Third, the *in vitro/in vivo* relationship for a solid oral dosage form is the result of interaction between the sensitivity to erosion of the formulation and the GI destructive force. Thus, in studies of oral dosage forms, we should investigate not only the effects of pH and surfactants on drug dissolution, but also the sensitivity to destruction of the dosage form, especially if it is a controlled-release product. In conclusion, the presence of destructive force and a low hydrodynamic flow are essential conditions for establishing a useful *in vitro* dissolution testing system.

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REFERENCES AND NOTES

1. N. Aoyagi, H. Ogata, N. Kaniwa, A. Ejima. Bioavailability of indomethacin capsules in humans(II): correlation with dissolution rate. *Int. J. Clin. Pharmacol. Ther. Toxicol.* 23: 529–534 (1985).
2. R. Dietrich, R. Brausse, G. Benedikt, V. W. Steinijans. Feasibility of in-vitro/in-vivo correlation in the case of a new sustained-release theophylline pellet formulation. *Arzneim.-Forsch.* 38: 1229–1237 (1988).
3. G. Levy, J. R. Leonards, J. A. Procknal. Development of *in vitro* dissolution tests which correlate quantitatively with dissolution rate-limited drug absorption in man. *J. Pharm. Sci.* 54: 1719–1722 (1963).
4. Z. Hussein and M. Friedman. Release and absorption characteristics of novel theophylline sustained-release formulations—*In vitro-in vivo* correlation. *Pharm. Res.* 7: 1167–1171 (1990).
5. M. Nicklasson, C. Graffner and M. I. Nilsson. Assessment of *in vivo* drug dissolution by means of numerical deconvolution considering gastrointestinal availability. *Int. J. Pharm.* 40: 165–171 (1987).
6. N. Aoyagi, H. Ogata, N. Kaniwa, M. Koibuchi, T. Shibazaki, A. Ejima, N. Tamaki, H. Kamimura, Y. Katougi, and Y. Omi. Bioavailability of griseofulvin from tablets in beagle dogs and correlation with dissolution rate and bioavailability in humans. *J. Pharm. Sci.* 71: 1169–1172 (1982).

7. N. Kohri, H. Yatabe, K. Iseki, K. Miyazaki. A new type of a pH-independent controlled release tablet, *Int. J. Pharm.* 68: 255–264 (1991).
8. S. K. E-Arini, G. K. Shiu, and J. P. Skelly. Theophylline-controlled release preparations and fatty food—An *in vitro* study using the rotating dialysis cell method. *Pharm. Res.* 7: 1134–1140 (1990).
9. C. Adithan, J. Thangam. A comparative study of saliva and serum paracetamol levels using a simple spectrophotometric method, *Br. J. Clin. Pharmacol.* 14: 107–109 (1982).
10. K. Iga, Y. Ogawa, T. Yashiki, T. Shimamoto. Estimation of drug absorption rates using a deconvolution method with nonequal sampling times. *J. Pharmacokinet. Biopharm.* 14: 213–225 (1986).
11. D. Verotta. An Inequality-constrained least-squares deconvolution method. *J. Pharmacokinet. Biopharm.* 17: 269–289 (1989).
12. K. Yamaoka, T. Tanigawara, T. Nakagawa, T. Uno. A pharmacokinetic analysis program (MULTI) for microcomputer. *J. Pharmacobio-Dyn.* 4: 879–885 (1981).
13. J. B. Dressman. Comparison of canine and human gastrointestinal physiology. *Pharm. Res.* 3: 123–131 (1986).
14. T. Kimura, K. Sudo, Y. Kanezaki, K. Miki, Y. Takeichi, Y. Kurosaki, T. Nakayama: Drug absorption from large intestine: Physicochemical factors governing drug absorption. *Biol. Pharm. Bull.* 17: 327–333 (1994).
15. H. Ogata, N. Aoyagi, N. Kaniwa, M. Koibuchi, T. Shibazaki, A. Ejima. Bioavailability of nalidixic acid from uncoated tablets in humans—part II: Bioavailability in beagle dogs and its correlation with bioavailability in humans and *in vitro* dissolution rates. *Int. J. Clin. Pharmacol. Ther. Toxicol.* 22: 240 (1984).
16. S. Aoki, K. Uesugi, K. Tatsuishi, H. Ozawa and M. Kayano. Evaluation of the correlation between *in vivo* and *in vitro* release of phenylpropanolamine HCl from controlled-release tablets. *Int. J. Pharm.* 85: 65–73 (1992).
17. H. Ogata, T. Shibazaki, T. Inoue and E. Ejima. Dissolution system for chloramphenicol tablet bioavailability. *J. Pharm. Sci.* 68: 712–715 (1979).
18. H. Ogata, N. Aoyagi, N. Kaniwa and A. Ejima. Effect of food on bioavailability of metronidazole from sugar-coated tablets having different dissolution rates in subjects with low gastric acidity. *Int. J. Clin. Pharmacol. Ther. Toxicol.* 24: 279–282 (1986).
19. J. Drewe, M. Keck, P. Guitard, A. Pellet, B. Johnston and C. Beglinger. Relevance of pH dependency on *in vitro* release of bromocriptine from a modified-release formulation. *J. Pharm. Sci.* 80: 160–163 (1991).
20. J. Drewe and P. Guitard. *In vitro-In vivo* Correlation for Modified-Release Formulations. *J. Pharm. Sci.* 82: 132–137 (1993).
21. P. Mojaverian, E. Radwanski, C. C. Lin, P. Cho, W. A. Vadino and J. M. Rosen. Correlation of *in vitro* release rate and *in vivo* absorption characteristics of four chlorpheniramine maleate extended-release formulations. *Pharm. Res.* 9: 450–456 (1992).
22. K. H. Yuen, A. A. Desmukh and J. M. Newton. *In vivo/in vitro* correlation of experimental sustained-release theophylline formulations. *Pharm. Res.* 10: 588–592 (1993).
23. D. Brockmeier, H. J. Dengler and D. Voegele. *In vitro-in vivo* correlation of dissolution, a time scaling problem? Transformation of *in vitro* results to the *in vivo* situation, using theophylline as a practical example. *Eur. J. Pharmacol.* 28: 291–300 (1985).