Gastric Emptying Rates of Drug Preparations. I. Effects of Size of Dosage Forms, Food and Species on Gastric Emptying Rates

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The gastric emptying rates of oral dosage forms of different sizes were studied in humans and beagle dogs measuring of marker drugs such as acetaminophen, aspirin and pyridoxal phosphate in plasma or urine. The marker drugs, except acetaminophen, were contained in enteric-coated granules or tablets which did not dissolve in the stomach but dissolved rapidly in the upper intestine. The gastric emptying rate of a dosage form of smaller size was faster than that of a larger size. The gastric emptying rates of dosage forms with different sizes did not correlate with each other inter-individually. The gastric emptying rates of dosage forms of any size were delayed when drugs were administered after taking a meal. The gastric emptying rates of dosage forms were extremely prolonged in beagle dogs after drug administration postprandially, and this restricted the use of beagle dogs as an animal model in bioavailability tests.

Keywords — gastric emptying rate; enteric-coated granule; enteric-coated tablet; human; beagle dog; dosage form size; meal; marker drug

Introduction

Although the pH-partition theory was established by Shanker *et al.*¹⁾ the stomach is not an important site for absorption, even for weak acid drugs. Most drugs are absorbed mainly in the intestine due to its extremely large area for absorption, and thus the gastric emptying rate of a drug administered orally affects the rate at which the drug is absorbed and delivered to its active sites. The gastric emptying rate is influenced by physiological conditions, diseases and drugs coadministered and foods taken simultaneously.²⁾ The gastric emptying of pharmaceutical preparations is influenced not only by these effects but also by their own physical properties such as particle size, and density.^{3,4)} Furthermore, the gastric emptying rate varies among animal species.^{5,6)}

The gastric emptying rate has been measured by various methods, such as using X-ray,⁷⁾ γ -camera,⁸⁾ a radiotelemetric capsule,⁹⁾ and aspiration of the residue in the stomach.¹⁰⁾ These methods, however, require expensive instruments or special techniques. On the other hand, the gastric emptying rate correlates with the plasma concentration of acetaminophen administered orally¹¹⁾ and the drug has been used for

measuring the gastric emptying rate by clinicians.¹²⁾ The plasma level of a marker drug contained in a formulation designed to release the drug in the upper intestine rather than in the stomach may also be used for determination of the gastric emptying rate.

Recently, many oral controlled-release products have been developed. A controlled-release product is required to release a drug at the expected rate before passing through the absorption site. Therefore, it should be very valuable to learn the characteristics of the gastric emptying rates of various types of oral dosage forms in order for research and development of oral controlled-release formulations.

We measured the gastric emptying rate of fine particles, granules and tablet forms, both in humans and beagle dogs, using marker drugs such as acetaminophen, aspirin and pyridoxal phosphate to determine the effects of size of dosage forms, food and species on the gastric emptying rate. Since different drugs were contained in dosage forms of different sizes, the gastric emptying rates of the different dosage forms could be measured by determinations of these drugs or their metabolites in plasma or in urine.

Materials and Methods

Materials — Acetaminophen (JP IX, Iwaki Pharmaceutical Co., Ltd., Lot No. 6xf081k), enteric-coated granules of aspirin (Shionogi Pharmaceutical Co., Ltd., Lot No. KE02) and an enteric-coated tablet of pyridoxal phosphate (Ohta Pharmaceutical Co., Ltd., Lot No. 10504) were commercial products in Japan. The enteric-coated granules of aspirin were of cylindrical shape, 0.7 mm in diameter and 1.5–3 mm in length. One gram contained 500 mg of aspirin. The diameter and thickness of the enteric-coated tablet used were 8 and 3.5 mm, respectively, and 10 mg of pyridoxal phosphate was contained in a tablet.

All other chemicals were of reagent grade.

Dissolution Rate — The dissolution rates of acetaminophen, aspirin and pyridoxal phosphate were measured by an oscillating basket method¹³⁾ using 900 ml of the first fluid of the disintegration test (pH 1.2, JP IX) and 0.1 M acetate buffer of pH 5.6. The concentrations of acetaminophen and pyridoxal phosphate in the test solution were determined at 300 and 390 nm respectively through a flow cell. In order to determine the dissolution rate of aspirin, 2 ml of the test solution were sampled periodically, then the solution filtered with a 0.8 μ m membrane filter was diluted with 0.1 N NaOH and the produced sodium salicylate was determined at 310 nm. A single dose was tested in an experiment using humans.

Bioavailability — Humans: Six healthy male volunteers, ages 22 to 35, weighing 55 to 73 kg, participated in the study. Informed consent was obtained from each subject. The gastric acidity of all subjects was found to be normal or high by the Gastro-test[®].¹⁴⁾ A one-way layout was employed for the following five treatments: acetaminophen, administration of 100 mg of acetaminophen powder in the fasting state; aspirin, administration of 200 mg of commercial enteric-coated granules of aspirin in the fasting state; pyridoxal phosphate, administration of an enteric coated tablet of pyridoxal phosphate in the fasting state, coadministration (F), coadministration of 100 mg of acetaminophen powder, 200 mg of aspirin enteric-coated

granules and an enteric-coated tablet of pyridoxal phosphate in the fasting state; and coadministration (NF), coadministration of the same drug products as those in coadministration (F) 30 min after a standard meal. The first three treatments are called Single in the Tables, and letters F and NF in the treatments of coadministrations mean administration in the fasting and nonfasting states, respectively.

The standard meal described in the previous report¹⁵⁾ was given to the subjects before drug administration in coadministration (NF). Urine samples were collected at 1, 2, 3, 4, 5, 6, 10, 13 and 22 h after drug administration. The onset of absorption of all drugs and maximum excretion occurred during the initial 6 h in all treatments. Subjects drank 100 ml of water in order to facilitate excretion of the urine and took the standard lunch at 4 h after drug administration. They were allowed to take drinks and food freely but were not allowed other drugs and alcohol. They were allowed to follow their usual workroutine but were not allowed to exercise.

Beagle Dogs: Eleven healthy male beagle dogs, weighing 8 to 13 kg were used. After overnight fasting, two capsules containing 100 mg of acetaminophen powder and 200 mg of enteric-coated granules of aspirin and an enteric coated tablet of pyridoxal phosphate were administered with 70 ml of water to five beagle dogs in the fasting state and to the remaining six different beagle dogs 30 min after feeding. The meal consisted of 250 g of CD 1 (Nihon Clea Co., Ltd.) and 50 ml of water. Four ml of blood were withdrawn at 0.25, 0.5, 1, 2, 3, 4, 6, 8 and 10 h after drug administration. Plasma was separated from 3 ml of blood for determination of acetaminophen and aspirin, and stored frozen until assay. One ml of whole blood was deproteinized with trichloroacetic acid, and after removal of trichloroacetic acid, using ether, the sample for determination of pyridoxal was stored frozen until assay.¹⁶⁾

Assay — Humans: Acetaminophen glucuronide and sulfate in urine were enzymatically hydrolyzed, and total acetaminophen was determined by a gas-chromatography method, hydrogen flame ionization detector-gas-liquid chromatography (FID-GLC). A mixture of 1 ml of

urine, 0.2 M acetate buffer (pH 5.0) and 0.1 ml of glucuronidase solution (β -glucuronidase activity 300000 — 400000 units, sulfatase activity 15000 — 40000 μ mol *p*-nitrocatechol/h/g, Sigma Chemical Co.) were incubated at 37 °C for 16 h. Two ml of 0.4 M phosphate buffer (pH 9.9) were added to the mixture and the hydrolyzed acetaminophen was extracted with 5 ml of ethylacetate. Four ml of the organic phase were evaporated to dryness, 0.2 ml of acetic acid anhydride in pyridine (2:5 v/v) was added to the residue, and the mixture was left at room temperature for 10 min. After removal of pyridine by evaporation, the residue was dissolved with 0.5 ml of acetone containing butyl acetaminophen as an external standard (0.5 mg/ml). Two μ l of the solution were injected into a gas-chromatography (Hitachi 163). Gas-chromatographic conditions were as follows; column, 2% polyethylene glycol/chromosorb W (3 mm $\times$ 2 m); column temperature, 200 °C; injection temperature, 218 °C, detector temperature, 205 °C.

All the salicylates and pyridoxic acid, one of the main metabolites of pyridoxal phosphate, excreted into urine were determined colorimetrically and fluorometrically according to the previous reports.^{15,17)}

Beagle Dogs: Free acetaminophen and salicylic acid in plasma were simultaneously determined by a high performance liquid chromatographic (HPLC) method. To 0.2 ml of plasma, 0.2 ml of 0.2 M acetate buffer (pH 5) and 5 ml of ethyl acetate were added. Four ml of the organic phase were evaporated under N₂ gas, and methanol containing 50 μ g/ml of theophylline as an external standard was added to the residue. Ten μ l of the aliquot were injected into a TSK GEL LS-410 (5 μ m, 4 mm $\times$ 25 cm) column which was developed with methanol-0.2 M phosphate buffer of pH 7.0 (1:4, v/v) at a flow rate of 1.0 ml/min. Acetaminophen and theophylline were detected at 244 nm (Jasco UVIDE C S-100-II) and salicylic acid was detected by a fluorescence spectrophotometer (Hitachi 650-60) at 438 nm with excitation at 358 nm.

Pyridoxal in whole blood was determined fluorometrically by a method previously reported.¹⁶⁾

Statistical Analyses — The lag time (t_{lag})

for the appearance of drugs or metabolites in plasma or urine and the mean absorption time (MAT) were used as parameters representative of gastric emptying rate. The estimation of t_{lag} was done by fitting plasma or urine data to an apparent one-compartment model with first-order absorption using PKM-MULTI, a nonlinear least square program.¹⁸⁾ MAT was calculated as follows,¹⁹⁾

$$\text{MAT} = \text{MRT} - 1/k_{\text{el}}$$

where MRT is the mean residence time²⁰⁾ and k_{el} is the apparent elimination rate constant after oral administration. These parameters were statistically subjected to analysis of variances (ANOVA) in the human study and to the student's *t*-test in the beagle dog study. Dunnett's multiple range test was done if required.

The other pharmacokinetic parameters such as the peak plasma concentration (C_{max}) and peak excretion rate (V_{max}) of drugs or metabolites, area under the curve (AUC_{∞}), urinary excretion amount of metabolites to infinite time (E_{∞}) were also statistically analyzed, although these parameters did not represent the gastric emptying rate.

MRT and AUC were calculated by a trapezoidal rule and the infinite values of MRT, AUC_{∞} and E_{∞} were calculated according to the method previously reported.^{21,22)}

Results and Discussion

The dissolution rates of marker drugs used are summarized in Table I. In the previous study,²³⁾ an enteric-coated tablet with a critical dissolution pH of 5.5 (the lowest pH where an enteric-coated tablet dissolves) was found to dissolve rapidly in subjects at any level of gastric acidity once it was transferred into the intestine. Thus, the enteric-coated granules of aspirin and tablet of pyridoxal phosphate with a critical dissolution pH value of 5.5 were chosen from commercial products, in order to determine the gastric emptying rates of granules and tablets. As previously mentioned, acetaminophen has been often used clinically as a marker for measuring the gastric emptying rate and, in the present

TABLE I. Physicochemical and Pharmaceutical Characteristics of Formulations

Drug	Dosage form	t_{50} (min)	
		pH 1.2	pH 6.8
Acetaminophen	Powder ^{a)}	1.5	2.0
Aspirin	Granules	— ^{b)}	7.8
Pyridoxal phosphate	Tablet	—	24.3

^{a)} Powder was not an enteric-coated formulation. Other formulations were enteric-coated. ^{b)} No dissolution was detected within 2 h.

work, acetaminophen administered as powder was also used as a marker. As shown in Table I, the values of t_{50} (the time required to dissolve 50% of the amount of acetaminophen) at pH 1.2 and 5.5 by the oscillating basket method were 1.5 and 2 min, respectively. This suggests that acetaminophen was emptied from the stomach in a solution, and thus acetaminophen was considered to be a marker of the gastric emptying rate of a solution rather than that of powder in this work.

t_{lag} and MAT were used for estimating the gastric emptying rates, although these parameters contain the time required to dissolve and to be absorbed in addition to the gastric emptying time. However, the time required for the drugs

to be absorbed may be very short in comparison to the other steps.²⁴⁾ Mojaverian *et al.*²⁵⁾ reported that a linear significant correlation was recognized between t_{lag} in aspirin absorption and the gastric residence time of the Heidelberg capsule in humans, which suggests that t_{lag} is a parameter highly related to the onset of gastric emptying of dosage forms.

Although the sum of metabolites in the urine was measured in this work, an excretion rates-time curve of each drug, after administration, followed an apparent one-compartment model with first-order absorption, and the t_{lag} obtained in this work was considered to represent the lag time for absorption, theoretically. The MAT obtained may include the time for metabolism

TABLE II. Pharmacokinetic Parameters of Marker Drugs in Humans (Mean $\pm$ S.D.)

Drug	Parameter	Single (S) ^{a)}	Coadministration (F) ^{b)}	Coadministration (NF) ^{c)}
Acetaminophen (Powder)	t_{lag} (h)	0.17 $\pm$ 0.16	0.12 $\pm$ 0.11	0.37 $\pm$ 0.07 ^{d)}
	MAT (h)	0.92 $\pm$ 0.13	1.31 $\pm$ 0.28	2.60 $\pm$ 0.21 ^{e)}
	V_{max} (mg/h)	13.74 $\pm$ 2.93	13.89 $\pm$ 2.12	13.02 $\pm$ 2.13
	E_{∞} (mg)	78.09 $\pm$ 12.72	84.54 $\pm$ 21.22	80.09 $\pm$ 12.33
	k_{el} (h ⁻¹)	0.264 $\pm$ 0.095	0.252 $\pm$ 0.110	0.263 $\pm$ 0.110
Aspirin (Granules)	t_{lag} (h)	1.14 $\pm$ 0.58	0.93 $\pm$ 0.31	1.21 $\pm$ 1.11
	MAT (h)	3.21 $\pm$ 0.12	3.94 $\pm$ 0.46	4.61 $\pm$ 0.28
	V_{max} (mg/h)	16.50 $\pm$ 2.65	16.62 $\pm$ 2.21	16.85 $\pm$ 2.42
	E_{∞} (mg)	91.55 $\pm$ 8.05	89.65 $\pm$ 12.46	91.12 $\pm$ 8.06
	k_{el} (h ⁻¹)	0.377 $\pm$ 0.098	0.436 $\pm$ 0.126	0.425 $\pm$ 0.119
Pyridoxal phosphate (Tablet)	t_{lag} (h)	1.43 $\pm$ 0.24	1.65 $\pm$ 0.58	3.31 $\pm$ 0.81 ^{e)}
	MAT (h)	2.81 $\pm$ 0.19	3.38 $\pm$ 0.48	6.02 $\pm$ 1.55 ^{e)}
	V_{max} (mg/h)	1.333 $\pm$ 0.559	0.992 $\pm$ 0.199	1.725 $\pm$ 0.426 ^{e)}
	E_{∞} (mg)	2.997 $\pm$ 0.559	2.982 $\pm$ 0.466	3.591 $\pm$ 0.504
	k_{el} (h ⁻¹)	0.662 $\pm$ 0.032	0.673 $\pm$ 0.190	0.724 $\pm$ 0.257

^{a)} Each drug was administered separately. ^{b)} In the fasting state. ^{c)} In the nonfasting state. ^{d)} Significantly different from F by Dunnet's multiple range test at $p = 0.05$. ^{e)} Significantly different from F by Dunnet's multiple range test at $p = 0.01$.

TABLE III. Correlation Coefficients of Parameters for Estimating Gastric Emptying Rate between Different Dosage Forms

Parameter	Dosage form	Powder		Tablet	
		F <i>a)</i>	NF <i>b)</i>	F	NF
t_{lag}	Granules	0.028	-0.608	-0.749	0.454
	Tablet	0.492	0.123		
MAT	Granules	-0.903	0.382	0.014	-0.588
	Tablet	-0.146	0.404		

a) Coadministration in the fasting state. *b)* Coadministration in the nonfasting state.

some extent, but the difference of MAT of the same drug between treatments represents the true difference in the absorption phase. The doses used in this work, including aspirin, were in the range where linear elimination was maintained.^{17,26,27)}

Effect of Coadministration of Three Drugs on Pharmacokinetic Parameters in Humans

The pharmacokinetic parameters of three drugs are summarized in Table II. Coadministration of acetaminophen, aspirin and pyridoxal phosphate did not affect the gastric emptying rates of dosage forms and the pharmacokinetic parameters of these drugs because there were no significant differences in the parameter

values of each drug between treatments of separate administration (acetaminophen, aspirin and pyridoxal phosphate) and coadministration (F). Thus by the coadministration method we could determine properly the gastric emptying rates of a solution, granules and a tablet simultaneously in a subject.

Correlation of Gastric Emptying Rates among Different Dosage Forms

There seems to be no correlation of the gastric emptying rates among the three dosage forms in humans after drug administration both in the fasting and nonfasting states (Table III). Because the ranges of the gastric emptying rates after administrations of these dosage forms were

Fig. 1. Excretion Rate-Time Curves of Metabolites after an Administration of Acetaminophen in Powder, Aspirin in Enteric-Coated Granules or Pyridoxal Phosphate in an Enteric-Coated Tablet in the Fasting and Nonfasting States in Humans

a) Solution (acetaminophen), b) granules (aspirin), c) tablet (pyridoxal phosphate). Solid line: in the fasting state, dotted line: in the nonfasting state.

relatively narrow, it was difficult to obtain good correlation.

Because pyridoxal phosphate was not absorbed from the enteric-coated tablet in one out of five beagle dogs, correlation coefficients could not be calculated in the beagle dog study. However, the t_{lag} and MAT values were significantly correlated between the solution (acetaminophen) and the granules (aspirin) in four beagle dogs where absorption of pyridoxal was recognized ($r = 0.958$ and $r = 0.994$).

These results suggested that under normal conditions the different dosage forms emptied from the stomach independently. There are no model formulations representing the gastric emptying rates for all dosage forms.

Effect of Size of Dosage Forms on Their Gastric Emptying Rates

The t_{lag} and MAT values of the solution (acetaminophen) were much shorter than those of granules (aspirin) and the tablet (pyridoxal phosphate). Thus, the gastric emptying rate of a solution was also shown to be very rapid in this work.

Although the gastric emptying rate of various dosage forms did not correlate with each other,

large size dosage forms seemed to be emptied more slowly (Table II).

Effect of Food on Gastric Emptying Rates of Drugs in Humans

As shown in Fig. 1, the excretion rate-time curves after drug administrations postprandially were shifted to the right. The t_{lag} and MAT values in the nonfasting states were increased in comparison with those in the fasting states (Table II). The differences in the t_{lag} and MAT values between these two treatments [coadministrations (F) and (NF)] were 0.25 and 1.29 h for solution (acetaminophen), and 0.28 and 0.70 h for granules (aspirin), respectively. The MAT and t_{lag} values for the tablet were also higher in the nonfasting state than those in the fasting state, although one subject showed a very rapid absorption with a lag time of 0.53 h even in the nonfasting state [This is the reason why double peaks appeared in the excretion rates-time curve of pyridoxic acid in the coadministration (NF)]. The differences in the parameter values between the fasting and nonfasting states in granules were relatively smaller than in the tablet. Although these data suggest that food delays the gastric emptying rates of

Fig. 2. Plasma Concentration-Time Curves of Drugs and Metabolites after Administrations of Acetaminophen in Powder, Aspirin in Enteric-Coated Granules and Pyridoxal Phosphate in an Enteric-Coated Tablet in the Fasting and Nonfasting States in Beagle Dog

a) Solution (acetaminophen), b) granules (aspirin), c) tablet (pyridoxal phosphate). Solid line: in the fasting state, dotted line: in the nonfasting state.

TABLE IV. Pharmacokinetic Parameters of Each Drug in Beagle Dogs

Drug	Parameter	Fasting	Nonfasting	<i>t</i> -Test
Acetaminophen (Powder)	t_{lag} (h)	0.23 $\pm$ 0.17 ^{a)}	0.29 $\pm$ 0.12	n.s. ^{b)}
	MAT (h)	0.68 $\pm$ 0.42	1.30 $\pm$ 0.56	n.s.
	C_{max} ($\mu\text{g/ml}$)	3.45 $\pm$ 1.83	1.74 $\pm$ 0.51	n.s.
	AUC ($\mu\text{g}\cdot\text{h/ml}$)	5.596 $\pm$ 3.120	5.161 $\pm$ 2.128	n.s.
	k_{el} (h^{-1})	1.04 $\pm$ 0.36	0.71 $\pm$ 0.17	n.s.
Aspirin (Granules)	t_{lag} (h)	0.98 $\pm$ 0.59	— ^{c)}	
	MAT (h)	3.35 $\pm$ 2.02	—	
	C_{max} ($\mu\text{g/ml}$)	28.41 $\pm$ 7.59	—	
	AUC ($\mu\text{g}\cdot\text{h/ml}$)	169.53 $\pm$ 51.22	—	
	k_{el} (h^{-1})	0.233 $\pm$ 0.430	—	
Pyridoxal phosphate (Tablet)	t_{lag} (h)	1.24 $\pm$ 0.51	—	
	MAT (h)	2.06 $\pm$ 0.55	—	
	C_{max} ($\mu\text{g/ml}$)	0.777 $\pm$ 0.366	—	
	AUC ($\mu\text{g}\cdot\text{h/ml}$)	3.136 $\pm$ 1.811	—	
	k_{el} (h^{-1})	0.298 $\pm$ 0.052	—	

a) Mean $\pm$ S.D. b) Not significant at $p = 0.05$. c) Not calculated because of incompleteness of absorption.

various drug preparations tested, the delays of the gastric emptying rate of granules were relatively short.

Differences in Gastric Emptying Rates between Humans and Beagle Dogs

The plasma levels of the drug-time curves in the fasting and nonfasting states are shown in Fig. 2 and the pharmacokinetic parameters are shown in Table IV. These data showed that, in the fasting state, the gastric emptying rate of the solution was faster than that of granules and the tablet in beagle dogs. The values of the gastric emptying rate parameters of the three preparations in beagle dogs were similar to those in humans.

In the nonfasting state, both values of t_{lag} and MAT for estimating the gastric emptying rate of acetaminophen in beagle dogs were slightly longer than those in the fasting state, although the differences were not statistically significant. On the other hand, as shown in Fig. 2, the plasma levels of salicylic acid were still rising at 10 h after postprandial administration and there was no evidence for absorption of pyridoxal phosphate. In humans, at 10 h after postprandial administration, the elimination rates of metabolites of both drugs had already decreased to the same levels after administrations in the fasting state. These data suggested that the gastric

emptying rates of granules and tablets were delayed longer by feeding in beagle dogs than in humans. In another report, an enteric-coated tablet was found to remain in the stomach 12 to 15 h after postprandial administration when hunger contractions occurred.²⁸⁾ Large particles greater than 5 mm were emptied from the stomach associated with the interdigestive migratory myoelectric complex which occurred about 7.5 h after feeding in beagle dogs.²⁹⁾ This may be a reason why the gastric emptying rates of granules and tablets were delayed so long in the beagle dog study. The solution, after drug administration in the nonfasting state, seemed to pass through the stomach into the intestine, regardless of such movement of the gastrointestinal in beagle dogs. Thus, the extremely prolonged gastric emptying rates of dosage forms in beagle dogs after feeding restrict their use in bioavailability tests as animal model.

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