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Gastrointestinal transit of non-disintegrating solid formulations in humans

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Summary

Gastrointestinal transit times of four non-disintegrating formulations, namely, heavy tablets (H-tablets; 8 × 4 mm; relative density 1.33), light tablets (L-tablets; 10 × 6 mm; relative density 0.86), pellets (2 × 5–6 mm; relative density 1.46) and micro-particles (420–590 μm; relative density 1.26), were studied in healthy subjects after a light breakfast using dual-isotope scintigraphy, and also under fasting conditions for H- and L-tablets. The gastroinestinal transit times of the tablets, pellets and micro-particles, which had a relative density of more than unity, were almost identical. The mean gastric emptying times (GET1/2; time for 50% activity to leave the stomach) of the formulations (H-tablets, pellets and micro-particles) were 2.7, 2.2 and 2.3 h, respectively, under non-fasting conditions. A large inter-subject difference was observed in arrival time to the colon (ATC1/2; time for 50% activity to arrive at the ascending colon after GET1/2) with a range of 1.5 h to more than 6.5 h with these formulations under non-fasting conditions. However, the time for 50% activity to arrive at the ileocecal junction after GET1/2 (small intestine transit time; SITT1/2) showed very small intersubject variations with mean values of 1.7, 2.6 and 1.9 h for H-tablets, pellets and micro-particles, respectively, under non-fasting conditions. The residence times for these formulations at the ileocecal junction were observed to be more than 2 h. Tablets having a relative density of less than unity (L-tablets) showed a significantly prolonged gastric emptying time in the non-fasting state in comparison with H-tablets, although both were emptied rapidly in the fasting state without any significant difference. The intestinal transit time of the L-tablets showed no difference from that of the H-tablets, irrespective of the administration conditions.

Introduction

The bioavailability of a drug administered orally may be affected by the gastrointestinal transit time of the preparation in addition to the dissolution rate of the drug from the preparation, especially from controlled-release preparations. For an enteric-coated preparation, the gastric emptying time is the predominant factor affecting the rate of bioavailability, and this in turn depends not only on physiological factors such as meal intake, disease state and posture but also on pharmaceuti-

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cal factors such as particle size and density (Nimmo, 1979). Sustained-release oral preparations have been extensively developed recently because of their various advantages for clinical application. The gastrointestinal transit time is one of the factors determining the duration of the clinically effective period and bioavailability of the drug, since some drugs have a restricted absorption site in the gastrointestinal tract.

The in vivo behavior of various types of drug delivery system has been monitored using gamma-scintigraphy for pellets (Bechgaard et al., 1985; Hardy et al., 1985), controlled-release pellets (Davis et al., 1987), tablets (Sangekar et al., 1987), controlled-release tablets (Davis et al., 1986) and osmotic tablets (Wilson et al., 1985). This technique has also been used successfully for characterizing the propulsive and/or contractile activity of the esophagus (Llamas-Elvira et al., 1986), stomach (Moore et al., 1983), small intestine (Malagelada et al., 1984) and colon (Krevsky et al., 1986). However, the gastrointestinal transit times of these reported solid dosage forms were examined under various experimental states. Therefore, a direct comparison of the transit time in one study with that in another is difficult.

In this study, comprising three investigations, the effects of particle size on gastrointestinal transit time of solid preparations were studied in a non-fasting state, and that of relative density under fasting and non-fasting conditions. Throughout these studies, a standard formulation was administered simultaneously with another in order to correct for inter-experimental variation, and gastrointestinal transit was monitored using a dual-isotope scintigraphy technique.

Materials and Methods

Preparation of radiolabelled formulations

Four radiolabelled non-disintegrating formulations were prepared (Table 1 and Fig. 1). The heavy (H) tablets consisted of 99.5% Lactose G® (Freund, Japan) and 0.5% magnesium stearate. The light (L) tablets consisted of 85% Luburi wax 101® (Freund) and 15% Sankilite® (Sanki, Japan). Both tablets (H and L) were coated with ethylcellulose so that they would not disintegrate at any pH. A solution of [^{131}I]iodine (yield 7 μCi per tablet) or [^{99m}Tc]pertechnetate (yield 50 μCi) was introduced via a small hole drilled at the center of each tablet. After drying, the hole was sealed with an epoxy resin adhesive (Aron-alpha®, Konishi, Japan). The pellets consisted of polyethylene tubes (Makiguchi Rubber, Tokyo) of diameter 2 mm and length 5–6 mm. Each pellet contained 40 μCi [^{99m}Tc]pertechnetate and a small metallic ball to control its density. Both ends of the tube were fused by heating. A cationic ion-exchange resin

TABLE 1

Dosage forms used in this study

	Heavy tablet	Light tablet	Pellet	Micro-particle
Weight (mg)	186.9	326.4	28.5	–
Diameter (mm)	8.0	10.0	2.0	420–590 (μm)
Thickness (mm)	4.0	6.0	5.0–6.0 (length)	–
Relative density	1.33	0.86	1.46	1.26
Labelled isotope	^{131}I, ^{99m}Tc	^{111}In	^{99m}Tc	^{111}In

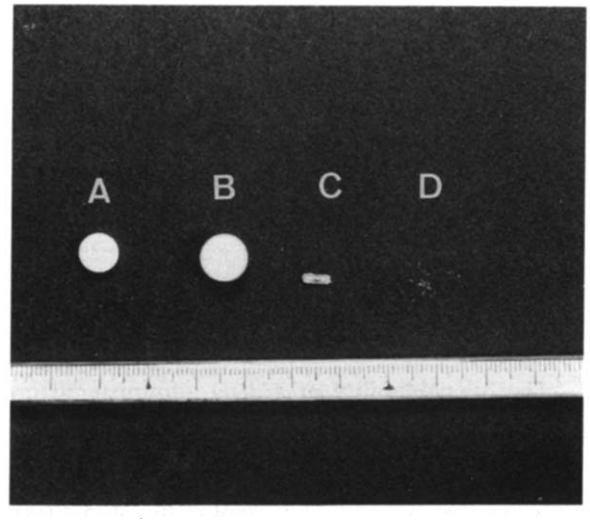

Fig. 1. Dosage forms used in this study. (A): H-tablet, (B): L-tablet, (C): pellet, (D): micro-particle.

(Dowex 50W-X4; 420–590 μm) was used as a form of micro-particle. A quantity (1 g) of the resin (Cl^- form) was mixed with ^{111}In solution (700 μCi) for 20 min, and unadsorbed ^{111}In was removed by washing and filtration. Radiolabelling of the formulations was performed immediately before administration.

Subjects

Three paneled studies (I–III) were carried out on three subject groups; (I) Eight males aged 20–27 years (weight range 59–74 kg); (II) five males aged 21–25 years (weight range 51–70 kg); (III) four males aged 20–22 years (weight range 54–70 kg). The subjects were healthy and were regular in their bowel habits, usually defecating once or twice a day. None was taking medication of any kind. Informed written consent was obtained from all subjects who participated in this study.

Administration

Study I. After an overnight fast, all volunteers had a light breakfast (80 g bread and 200 ml milk) at least 30 min before testing. Four H-tablets labelled with ^{99m}Tc and 1 g of resin labelled with ^{111}In were simultaneously administered with 200 ml water. A light lunch (400 g rice and 200 ml miso soup) was taken 4 h after dosing. Radioactivity was monitored until 7 h after administration.

Study II. Four H-tablets labelled with ^{131}I and four pellets labelled with ^{99m}Tc were simultaneously administered to five subjects with 200 ml water under the same conditions as for study I. Radioactivity was monitored until 10 h after administration.

Study III. Four L-tablets labelled with ^{111}In and four H-tablets labelled with ^{99m}Tc were simultaneously administered with 200 ml water under fasting and non-fasting conditions following a cross-over design with a 1 week interval. In the fasting experiment, the subjects fasted overnight for more than 12 h prior to and 4 h after oral administration of the tablets. The administration conditions for the non-fasting experiment were the same as for study I. Radioactivity was monitored until 10 h after administration.

Imaging of formulations

As anatomical reference markers, three pellets containing [^{99m}Tc]pertechnetate and ^{111}In were taped at both the iliac crest and xiphisternum. Imaging was carried out using a gamma-camera (LFOV, Searle, F.R.G.) with a diameter of 37 cm of the field of view and fitted with a medium-energy, 300 keV maximum parallel-hole collimator. The 140 keV photon emission of ^{99m}Tc, 360 keV emission of ^{131}I or 245 keV emission of ^{111}In were detected simultaneously but separately. Anterior images of tablets and pellets were taken in the standing position in front of the gamma-camera, and posterior images were also taken simultaneously when micro-particles were being administered. The data on microparticles labelled with ^{111}In were recorded on a computer (Scintipac 2400, Shimadzu, Japan), and the geometric mean of the anterior and posterior counts was taken as the activity which was approximately independent of the depth of the source (Hardy et al., 1985). Places where radioactivity was found on the scintigrams were enclosed in frames and the ratio of activity within each frame to the total was calculated. No interference from ^{99m}Tc was encountered in measurements. In contrast, since ^{111}In influenced the determination of both ^{99m}Tc and ^{131}I, these radionuclides were used as labels for tablets and pellets for the sole purpose of identifying the location and counting the number of preparations using scintigrams. ^{99m}Tc and ^{131}I could be distinguished according to their images, although they do interfere with each other. Views of 2 min duration were recorded every 30 min during the first 2 h and then every 30 min or/60 min over the test period.

Results

It was confirmed by in vitro and preliminary in vivo testing that no radioactivity within the formulations was released at all.

In study I, the gastrointestinal transit rates of two differently sized non-disintegrating formulations with a density greater than unity, H-tablets and micro-particles, were compared. Fig. 2 shows the scintiphotos of ^{99m}Tc-labelled H-tablets and ^{111}In-labelled micro-particles after co-administra-

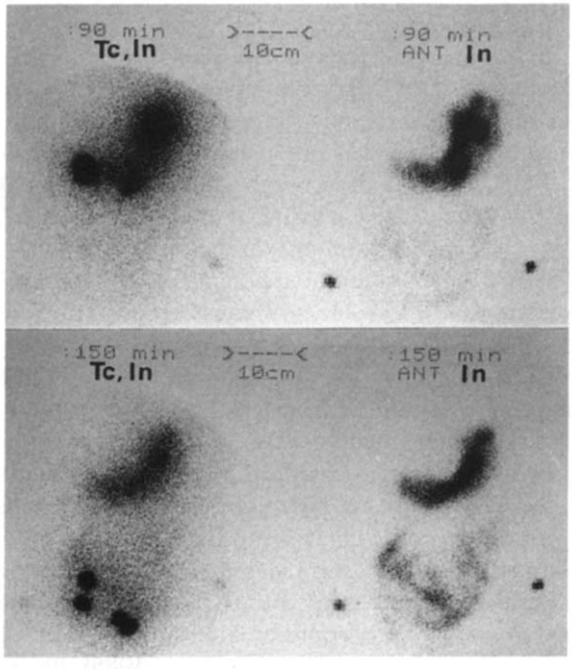

Fig. 2. Scintiphotos obtained after simultaneous administration of four heavy tablets and 1 g micro-particles to one subject in study I. (Left view) ^{111}In and ^{99m}Tc images have been superimposed. (Right view) ^{111}In image only.

tion to one subject. The left views are those of the 140 keV photon emission of ^{99m}Tc, and show images of ^{99m}Tc-labelled H-tablets on which

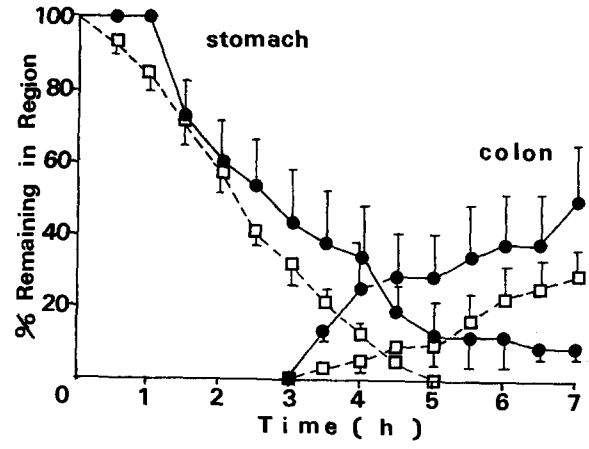

Fig. 3. Mean gastrointestinal transit of four heavy tablets (●———●) and 1 g micro-particles (□— — —□) in study I ($N = 8$, mean ± SE).

^{111}In-labelled microparticles are superimposed. On the other hand, those on the right depict views of the 245 keV photon emission of ^{111}In, and show only the image of ^{111}In-labelled micro-particles. Although all H-tablets administered were found to remain in the stomach at 90 min, some of the micro-particles had already been emptied from the stomach. At 150 min, the radioactivity was detected partially at both the ileocecal junction and the ascending colon.

TABLE 2

Gastrointestinal transit of heavy tablets and microparticles in study I

Subject no.	GET 1/2 (h)		ATC 1/2 (h)		SITT 1/2 (h)		RTI (h)	
	H	M	H	M	H	M	H	M
1	1.5	1.7	3.8	4.0	2.5	2.1	1.3	1.9
2	4.0	2.5	> 3.0	> 4.5	1.0	1.3	–	–
3	1.5	1.7	2.0	4.7	1.5	1.8	0.5	2.9
4	1.3	2.6	2.8	> 4.4	1.3	1.7	1.5	–
5	2.5	2.0	> 4.5	> 5.0	0.5	2.2	–	–
6	6.5	3.2	–	> 3.8	> 0.5	2.6	–	–
7	4.3	2.5	2.5	3.3	0.5	0.9	2.0	2.4
8	2.0	1.9	> 5.0	> 4.1	1.0	2.8	–	–
Mean	2.9	2.3	(2.8)	(4.0)	(1.2)	(1.8)	(1.3)	(1.8)
SE	0.6	0.2						
Paired *t*-test (formulation)	N.S.							

H, heavy tablet; M, micro-particle. Values in parentheses represent means for subjects showing definite values for both preparations administered.

Fig. 3 shows the mean time courses of the gastrointestinal transit of H-tablets and micro-particles in the different regions of the gastrointestinal tract. Table 2 lists the mean values of GET1/2, ATC1/2, SITT1/2 and RTI. GET1/2 denotes the time taken for 50% of the activity to leave the stomach, ATC1/2 being the time taken for 50% of the activity to arrive at the ascending colon after GET1/2. SITT1/2 is defined as the time taken for 50% of the activity to arrive at the ileocecal junction after GET1/2. RTI is the residence time of the formulation at the ileocecal junction, which is determined by subtracting SITT1/2 from ATC1/2. In five subjects out of eight, the ATC1/2 value could not be determined because more than 50% of the radioactive marker did not arrive at the ascending colon within 7 h after administration, indicating that the monitoring period of 7 h was too short. Therefore, the duration of monitoring was 10 h in studies II and III. No significant differences appeared in the mean values of GET1/2 (1.5–6.5 h), ATC1/2 (2.0–more than 5 h), SITT1/2 (0.5–2.8 h) and RTI (0.5–2.9 h) between H-tablets and micro-particles, as shown in Table 2. However the gastric emptying pattern showed clear differences between the formulations, i.e., the H-tablets clearly showed a time lag for gastric emptying in all cases observed (mean 1.69 h, range 1–4 h), whereas the micro-particles did not. Furthermore, inter-subject variation in gastric emptying for H-tablets was larger in comparison with that for the micro-particles.

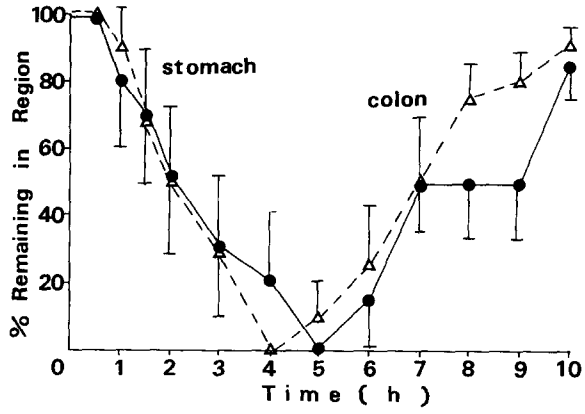

Fig. 4. Mean gastrointestinal transit of four heavy tablets (●———●) and four pellets (△— — —△) in study II ($N = 5$, mean ± SE).

Study II concerned the gastrointestinal transit rate of pellets (2 × 5–6 mm) under the same conditions as in study I. H-tablets were also co-administered for comparison with study I. The gastrointestinal transit rates of both formulations did not differ (Table 3 and Fig. 4). The transit rates of H-tablets had almost the same values as those in study I. Mean values of GET1/2 for H-tablets and pellets were 2.4 ± 0.7 h (mean ± SE) and 2.2 ± 0.4 h, respectively. Although ATC1/2 showed very large inter-subject variations ranging from 3.5

TABLE 3

Gastrointestinal transit of heavy tablets and pellets in study II

Subject no.	GET 1/2 (h)		ATC 1/2 (h)		SITT 1/2 (h)		RTI (h)	
	H	P	H	P	H	P	H	P
1	2.0	2.0	3.5	3.5	3.0	3.0	0.5	0.5
2	3.0	3.5	5.0	> 6.5	2.0	1.5	3.0	> 5.0
3	1.5	1.5	3.5	4.0	2.5	2.5	1.0	1.5
4	0.8	1.0	6.3	6.3	4.2	4.0	2.1	2.3
5	4.5	3.0	5.0	5.0	0.3	2.0	4.7	3.0
Mean	2.4	2.2	(4.6)	(4.0)	2.4	2.6	(2.0)	(1.8)
SE	0.7	0.4			0.6	0.4		
Paired *t*-test (formulation)	N.S.				N.S.			

H, heavy tablet; P, pellet. Values in parentheses represent means for subjects showing definite values for both preparations administered.

TABLE 4

Gastrointestinal transit of heavy tablets and light tablets in study III

Subject no.	GET 1/2 (h)		ATC 1/2 (h)		SITT 1/2 (h)		RTI (h)	
	H	L	H	L	H	L	H	L
Fasting conditions								
1	1.3	0.8	3.1	3.5	1.3	1.0	1.8	3.5
2	0.3	1.5	4.3	3.0	2.0	3.0	2.3	0
3	0.3	0.3	4.5	4.1	1.5	1.5	3.0	2.6
4	0.5	0.3	6.8	7.0	3.8	4.0	3.0	3.0
Mean	0.6	0.7	4.7	4.4	2.1	2.4	2.5	2.3
SE	0.3	0.3	0.8	0.9	0.6	0.7	0.3	0.8
Paired *t*-test (formulation)	N.S.		N.S.		N.S.		N.S.	
Non-fasting conditions								
1	2.3	5.0	6.0	> 5.3	1.3	1.3	4.7	–
2	3.0	4.8	1.5	4.5	0.5	1.0	1.0	3.5
3	3.8	6.5	5.8	> 3.5	0.8	1.0	5.0	–
4	1.5	6.5	4.0	> 4.6	1.0	2.1	3.0	–
Mean	2.6 [a]	5.7 [a]	(1.5)	(4.5)	0.9	1.3	(1.0)	(3.5)
SE	0.5	0.5			0.2	0.3		
Paired *t*-test (formulation)	$p < 0.05$				N.S.			

H, heavy tablet; L, light tablet. Values in parentheses represent means for subjects showing definite values for both preparations administered.[a] The values of GET 1/2 for H- and L-tablets were significantly prolonged ($p < 0.05$) after administration postprandially in comparison with those under fasting conditions.

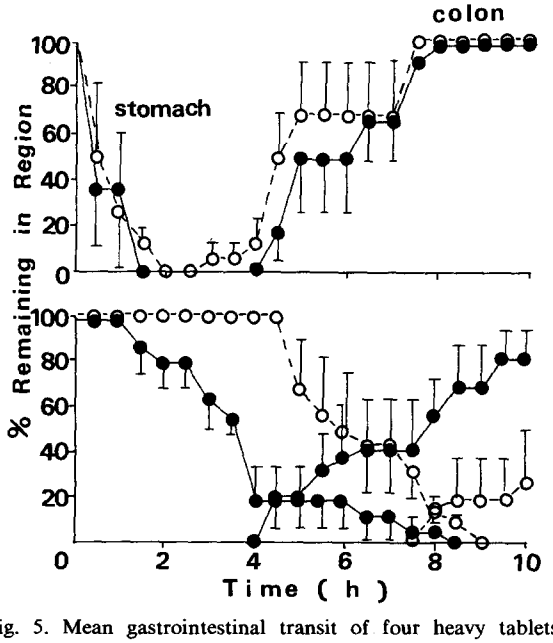

Fig. 5. Mean gastrointestinal transit of four heavy tablets (●———●) and four light tablets (○— — —○) in study III ($N = 4$, mean ± SE). (Upper panel) fasting conditions, (lower panel) non-fasting conditions.

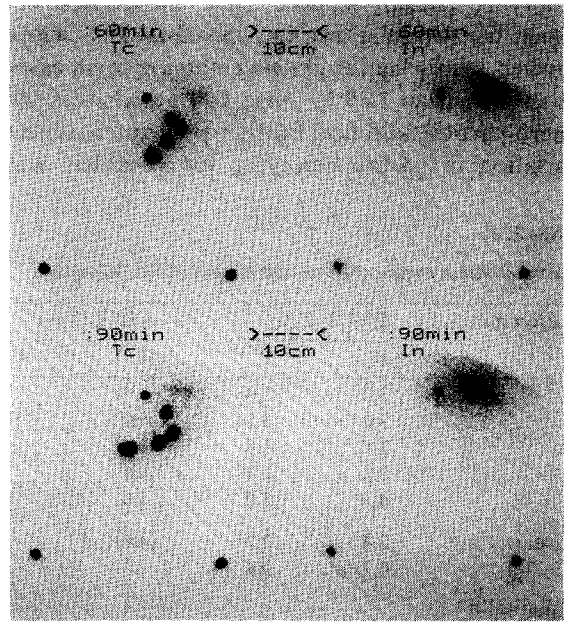

Fig. 6. Scintiphotos obtained after simultaneous administration of four heavy tablets (left) and four light tablets (right) to subject no. 2 under non-fasting conditions in study III.

h to more than 6.5 h for both formulations, SITT1/2 showed very small inter-subject variations with mean values of 2.4 ± 0.6 h and 2.6 ± 0.4 h for H-tablets and pellets, respectively. RTI ranged from 0.5 h to more than 5 h, which caused the large variation of ACT1/2.

A comparison of the transit rates of H-tablets and L-tablets is given in Table 4 and Fig. 5. The presence of food delayed the gastric emptying of the formulations in all cases. The mean values of GET1/2 for H- and L-tablets under fasting conditions were 0.6 ± 0.3 and 0.7 ± 0.3 h, respectively, i.e., not significantly different. However, under non-fasting conditions, the values of GET1/2 for H- and L-tablets were 2.6 ± 0.5 and 5.7 ± 0.5 h, respectively, demonstrating that gastric emptying of L-tablets was significantly prolonged under non-fasting conditions in comparison with H-tablets. Under non-fasting conditions, the L-tablets took up positions in the upper part of the stomach in contrast with H-tablets, which were located mostly in the lower areas, as shown in Fig. 6. These results appear to suggest that the prolonged gastric emptying of L-tablets under non-fasting conditions was due to their buoyancy. However, there was no significant difference in the values of ACT1/2, ITT1/2 and RTI between the formulations under both fasting and non-fasting conditions. These results show that tablets of relative density below unity may show prolonged gastrointestinal transit only when administered postprandially, which can be ascribed to the slower gastric emptying rate, in comparison with those having a relative density greater than unity.

Discussion

The gastrointestinal transit rate in the different regions of the gastrointestinal tract was represented by means of evaluating the parameters GET1/2, ATC1/2, SITT1/2 and RTI in this study. The gastrointestinal transit rate is commonly expressed as GET1/2 and ACT1/2 from the observed radioactivity-time curve after administration of a radionuclide as a liquid or semi-solid (Feldman et al., 1984; Christensen et al., 1985). On the other hand, in the case of a large-sized dosage form such as a tablet, capsule or pellet, the time until emptying from the stomach or that until appearance at the colon after administration of a unit dose is often used (Feldman et al., 1984; Davis et al., 1986, 1987). Both forms of expression appear to differ somewhat and are not directly comparable. Therefore in this study, multiple units of tablets or pellets were administered and the rate of transit was expressed in the same manner as for a solution or micro-particles, although the value may have included a relatively large error, as only four units were administered.

As already reported, GET1/2 is very variable, and is affected not only by the physical properties of the preparations such as particle size and density (Meyer et al., 1988), but also by physiological conditions such as fasting or non-fasting, amount and composition of meals (Han et al., 1982), posture (Yu, 1975) and disease (Feldman et al., 1984; Loo et al., 1984). The GET1/2 values observed in a non-fasting state in this study were very similar to those reported previously (Bechgaard et al., 1985; Davis et al., 1986). The means for GET1/2 in a non-fasting state did not vary significantly with particle size of preparations (8–0.5 mm) when the relative density was above unity. However, micro-particles (420–590 μm) emptied immediately after administration, in contrast to pellets (2 × 5–6 mm) and tablets (8 × 4 mm), which showed a clear time lag before emptying.

SITT1/2, the transit time from the upper part of the duodenum to the lower part of the ileum, was shown to be relatively short, around 2 h, with a small inter-individual variation, which did not appear to be correlated with the size and density of the preparations administered.

We included RTI in this study as a parameter for describing the gastrointestinal transit rate of solid preparations. Most solid preparations tended to remain irregularly at the terminal ileum, and did not flow backward once they had moved to the ascending colon. We speculated that the site was the ileocecal junction, as judged from the observations described above, not from anatomical corroboration. The ileocecal junction is considered to serve two purposes: prevention of both reverse flux of the colonic contents into the small intestine and of rapid passage of contents through

the ileum (Weisbrodt, 1981). This area exhibits many of the characteristics of a sphincter, opening when a peristaltic wave, passing along the terminal ileum, builds up enough pressure to overcome its resistance (Netter, 1979). RTI for the solid preparations was relatively variable among the subjects, irrespective of the physical properties of the preparations such as particle size and relative density. The mechanisms and factors controlling the passage of fluids and solids through the ileocecal junction still seem to be unclear, although the residence time should be considered when making a sustained release preparation.

Floating tablets of relative density lower than unity have recently received attention as a means of prolonging both gastric emptying and eventual drug absorption after oral administration. However, their effectiveness has not yet been confirmed (Davis et al., 1986; Ingani et al., 1987; Sangekar et al., 1987). L-tablets having a relative density of less than unity exhibited significantly prolonged gastric emptying when administered under non-fasting conditions, although they were emptied rapidly under fasting conditions with no difference on comparison with H-tablets. These results are consistent with those reported by Sangekar et al. (1987). Furthermore, there was no difference in SITT1/2, ACT1/2 and RTI between L- and H-tablets, irrespective of the administration conditions. These results suggest that light tablets are resistant to mild contractions in the stomach in the presence of food, but not to hunger contractions, especially phase 3 of the migrating myoelectric compex (MMC) under fasting conditions, and in the small intestine the types of behavior among tablets cannot be distinguished in terms of their density.

As described above, SITT1/2 was very short and less variable. In contrast, gastric emptying time and residence time at the ileocecal junction were relatively long and very variable. Thus, it may be concluded that the entire transit time of solid preparations from the stomach to the ascending colon is determined by the gastric emptying time and the residence time at the ileocecal junction. The residence time of solid preparations at the ileocecal junction seems to be independent of pharmaceutical factors and meal intake, although the gastric emptying of solid preparations is determined by these factors.

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