Variation in Gastrointestinal Transit of Pharmaceutical Dosage Forms in Healthy Subjects

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The variability in the gastrointestinal transit of a multiple-unit and single-unit dosage form was investigated following a light breakfast in six, healthy, male volunteers after repeated weekly administration. The dosage forms were labeled with gamma-emitting radionuclides and the transit of the formulations was monitored on 4 separate study days using the technique of dual-isotope gamma scintigraphy. Gastric emptying times and small intestinal transit times were calculated and compared statistically within and between subjects using the standard deviation and coefficient of variance. The variability in gastric emptying of single- and multiple-unit systems was large; the intrasubject variation being less than the intersubject. There was less variation in small intestinal transit times for the single- and multiple-unit formulations than in gastric emptying, intrasubject variation again being less than intersubject variation.

KEY WORDS: gamma scintigraphy; variability; gastrointestinal transit; pharmaceutical dosage forms.

INTRODUCTION

In 1976 gamma scintigraphy was first described as a suitable technique to study the *in vivo* fate of pharmaceuticals (1,2). Since then numerous studies have been carried out to evaluate the behavior of formulations within the gastrointestinal tract (3,4) and to investigate the pharmaceutical (5,6) and physiological (7,8) strategies for modifying their performance. Few studies to date have addressed the variability of gastrointestinal transit within and between individuals (9,10). Brophy *et al.* (9) investigated the variability of gastric emptying measurements in man employing standardized radiolabeled meals. They concluded that meal emptying is a variable phenomenon in healthy subjects with significant inter- and intrasubject day-to-day differences. These findings could have pronounced effects in the field of drug delivery. The recent trend to produce more sophisticated dosage forms has led to the emergence of pulsed or timed release devices. These are designed to deliver drug after a certain time to a specific area. If there is a great intrasubject variation in transit times, then their use may be precluded due to the unintentional delivery of drug to an inappropriate region of the gastrointestinal tract.

The present study was designed to explore the range and extent of intrasubject variation in the gastrointestinal transit of pharmaceutical formulations in six, healthy, male volunteers on 4 separate occasions. Using dual-isotope gamma scintigraphy it was possible to assess simultaneously the behavior of both single-unit and multiple-unit systems following concomitant administration. The protocol for this study was chosen to eliminate or, at best, reduce as many variables as possible, so that natural variation in gastrointestinal transit could be assessed.

MATERIALS AND METHODS

Labeled Pellets

Nonpariel cores were spray coated with a suspension of Amberlite IRA 410 (<90 μm) and subsequently overcoated with ethyl cellulose (11). The pellets were sieved to a size range of 0.8- to 1.1-mm diameter and labeled by mixing 3.5 g of resin (enough for 10 capsules) with 99M-technetium (Tc) using ^{99M}Tc sodium pertechnetate obtained from a generator (Amersham International). The labeled pellets were filled into size 2 hard gelatin capsules to a notional fill weight of approximately 330 mg to give an activity/capsule of approximately 4MBq ^{99M}Tc at the time of administration. Stability of the binding of the label to the ion-exchange resin was checked *in vitro* under relevant conditions of temperature and pH (12).

Labeled Tablets

Nondisintegrating tablets (approximate fill weight, 500 mg) were prepared from ethyl cellulose (BDH, Poole, Dorset) using 1.15-cm round, shallow concave punches. Prior to compression, the ethyl cellulose was mixed with a small quantity (10 mg) of Amberlite resin IR 120 (BDH, Poole, Dorset), density 1.2 g/cm^3, radiolabeled with 1 MBq 111-indium (In). The powder mix was then directly compressed into tablets using a Manesty F3 single-punch tablet machine. The tablets were coated to prevent the leaching out of the radiolabel and *in vivo* disintegration. The integrity of the tablets was checked *in vitro* under simulated conditions relevant to the gastrointestinal tract (12).

Subjects

The study was carried out on six, young, healthy males who were nonsmokers and were not on any medication (age, 21–23; height, 152–164 cm; weight, 64–83 kg.). Each volunteer gave written informed consent for the study to be performed. The experimental protocol was approved by the ethics committee of the University of Nottingham and conducted in accordance with the declaration of Helsinki guidelines for ethics in research. Approval to administer radiopharmaceuticals was obtained from the Department of Health.

Dosage Instructions and Diet

The subject's diet was strictly controlled throughout the study period. On the day prior to the study, the subjects took breakfast and lunch as normal; after lunch each subject fol-

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lowed the same protocol (Table I) for each week of the study.

Procedure

Small ^{111}In-labeled anatomical reference markers were taped to the skin anteriorly and posteriorly over the right lobe of the liver. At 9:00 AM each volunteer swallowed one labeled tablet and one capsule containing the labeled pellets with 100 ml of water. Immediately after dosing, simultaneous imaging of the abdomen (anterior and posterior views) was undertaken using a gamma camera (General Electric Maxicamera, Type II) having a 40-cm-diameter field of view and fitted with a medium-energy (300-keV maximum energy) parallel-hole collimator. Images of 60-sec duration were taken at intervals of approximately 15–20 min over a period of 12 hr and data recorded by computer (Nodecrest) for later analysis.

The study was repeated using exactly the same protocol on each of the 4 study periods separated by 1-week intervals to permit the assessment of intrasubject variation.

Data Representation

Dispersion of the pellets enabled delineation of the stomach and colon region, and the subsequent position of the single unit to be identified. Gastric emptying and colon arrival of the pellet formulations were established by defining regions of interest around the stomach and large intestine. Values for count rates in the defined regions of interest around the stomach and colon were obtained and the data corrected as described previously (6). The values subsequently calculated represented percentages of the total administered radioactivity and these were plotted against time to give transit profiles (Figs. 1 and 2). The data for the study are expressed in a number of different ways. Gastric emptying data are given as the time for 50% ($t_{50\%}$) of the pellets to empty the stomach and are shown in Table II. Small intestinal transit times are presented in Table III and are taken as the difference in time between 50% of the pellets arriving in the colon and 50% of the pellets leaving the stomach. Gastric emptying times for the single-unit dosage forms are given in Table IV. Unlike the pellet formulation the gastric emptying and colon arrival of single units is an all-or-nothing process, the images were therefore analyzed by noting the time of the image in which the tablet had emptied from the stomach or entered the colon. The small intestinal transit time (Table V) of the single-unit dosage form is taken as the difference between colon arrival and gastric emptying.

Table 1. Dietary Conditions

	Day prior to study
2 PM	From 2 PM the only food consumed was provided by the investigator
6 PM	Orange juice Prawn cocktail Steak, chips, and peas Cheesecake Coffee/tea
	Study day
8:15 AM	Orange juice Lightly buttered toast (2 slices) Coffee/tea
1 PM	Orange juice Two rolls (one ham, one cheese) Crisps (one bag) Coffee/tea
3 PM	Coffee/tea
6 PM	Orange juice Pizza (regular) Coffee/tea

Table II. Gastric Emptying Times (Minutes) for 50% of Multiple-Unit Dosage Forms

	Week						
Subject	1	2	3	4	Mean (X)	SD[a]	CV (%)[b]
1	94	154	151	142	135	28	21
2	23	28	47	23	30	11	38
3	64	74	92	106	84	19	22
4	113	88	122	177	125	38	30
5	99	156	120	147	131	26	20
6	146	154	94	109	126	29	23
Mean	90	109	104	117			
SD	42	54	35	53			

[a] Standard deviation.
[b] Coefficient of variation % = (SD/X) × 100.

RESULTS

Gastrointestinal Transit of the Multiple-Unit System

The pellets were released rapidly from the hard gelatin capsule, and the dispersion of the pellets enabled ready identification of the stomach region. After a light breakfast the pellets emptied from the stomach is an essentially randomised manner. For most subjects a lag phase in emptying was noted in which the pellets mixed with the food before emptying commenced. The mean gastric emptying time was 105 min (SD ± 45 min; n = 24), which is similar to that reported previously (13). Intersubject variation in gastric emptying ($t_{50\%}$) of the pellets was large with a range of 23–177 min. In

Table III. Small Intestinal Transit Times (Minutes) for 50% of Multiple-Unit Dosage Forms

	Week						
Subject	1	2	3	4	Mean (X)	SD[a]	CV (%)[b]
1	263	211	204	210	222	28	12
2	236	222	254	239	238	13	16
3	181	197	177	179	184	9	5
4	130	173	197	184	171	29	11
5	144	129	137	162	143	14	10
6	350	352	190	290	296	76	26
Mean	217	214	193	211			
SD	83	75	38	47			

[a] Standard deviation.
[b] Coefficient of variation % = (SD/X) × 100.

Table IV. Gastric Emptying Times (Minutes) for Single-Unit Dosage Forms

Subject	Week 1	2	3	4	Mean (X)	SD[a]	CV (%)[b]
1	68	83	100	120	93	22	24
2	34	51	103	51	60	30	50
3	51	84	86	192	103	61	59
4	69	85	138	83	94	30	33
5	86	136	85	118	106	25	24
6	86	118	69	67	85	24	28
Mean	66	93	97	105			
SD	20	30	24	51			

[a] Standard deviation.
[b] Coefficient of variation % = (SD/X) × 100.

comparison, the intrasubject variation was less, the smallest variation in gastric emptying for the pellet system being 24 min for subject 2 (range, 23–47 min) and the largest variation being 89 min for subject 4 (range, 88–177 min). The gastric emptying profiles (Figs. 1 and 2) do possess a notable consistency for each of the 4 study weeks. However, the coefficient of variation yields consistently large values of between 20 and 38%. The rate of gastric emptying was the main factor to affect the spread of pellets in the small intestine, and once the material had left the stomach there was little, if any, additional spreading. The mean small intestinal transit time was 209 min (SD ± 60 min, n = 24), which is in accord with the figure previously reported by Davis *et al.* (14) of 180 min (SD, ±60 min). Small intestinal transit times follow a similar trend to the gastric emptying results. The intersubject variation was large, with a range of 130–352 min. Intrasubject variation was less, the smallest variation in small intestinal transit time being 20 min (subject 2; range, 177–197 min) and the largest variation being 162 min (subject 6; range, 190–352 min). The coefficients of variation for small intestinal transit times (Table II) are consistently low.

The pellets which had spread in the small intestine were observed to regroup at the ileocecal junction before entering the cecum. In most cases entry of the pellets into the colon was as a bolus, which is illustrated in the relatively steep colon arrival profiles (Figs. 1 and 2).

Table V. Small Intestinal Transit Times (Minutes) for Single-Unit Dosage Forms

Subject	Week 1	2	3	4	Mean (X)	SD[a]	CV (%)[b]
1	223	267	181	222	223	35	16
2	240	207	195	216	215	19	9
3	157	192	179	94	156	44	28
4	176	174	161	183	174	9	5
5	51	172	36	91	88	61	20
6	207	371	196	165	235	93	39
Mean	176	231	158	162			
SD	68	77	61	58			

[a] Standard deviation.
[b] Coefficient of variation % = (SD/X) × 100.

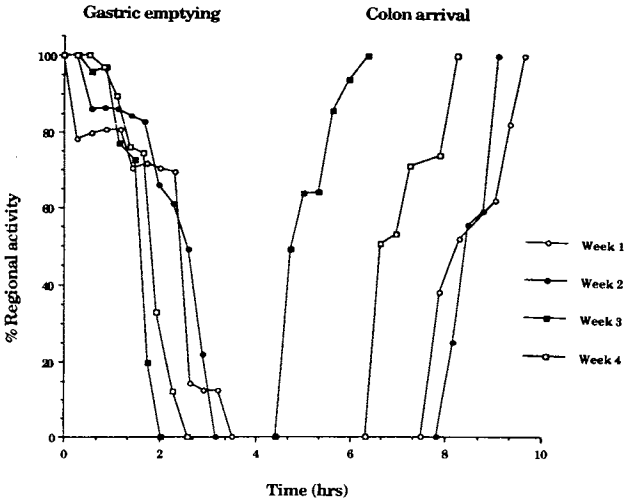

Fig. 1. Total transit profiles for volunteer 6.

Gastrointestinal Transit of the Single-Unit System

The tablet passed from mouth to anus intact in all the volunteers on each of the study days, thereby confirming the *in vitro* testing methodology. A mean gastric emptying time of 90 min (SD, ±35 min; n = 24) was obtained for the single-unit system. Contrary to previously published data (15), the single-unit emptied before all of the multiple-unit system had left the stomach. Intersubject variation in gastric emptying was large, with a range of 34–192 min. Intrasubject variation was less, the smallest variation in gastric emptying for the single unit being 50 min for subject 5 and the highest variation 141 min for subject 2. The coefficient of variation for the single-unit system is greater than for the multiple-unit system, with a maximum of 59%.

The small intestinal transit time was 182 min (SD ± 69 min; n = 24), which again is in accord with the value quoted by Davis et al. (14). Intersubject variation was large, with a range of 51–371 min, whereas intrasubject variation was less, the smallest variation being 22 min and the largest variation being 206 min for subject 6. In some subjects the single-unit

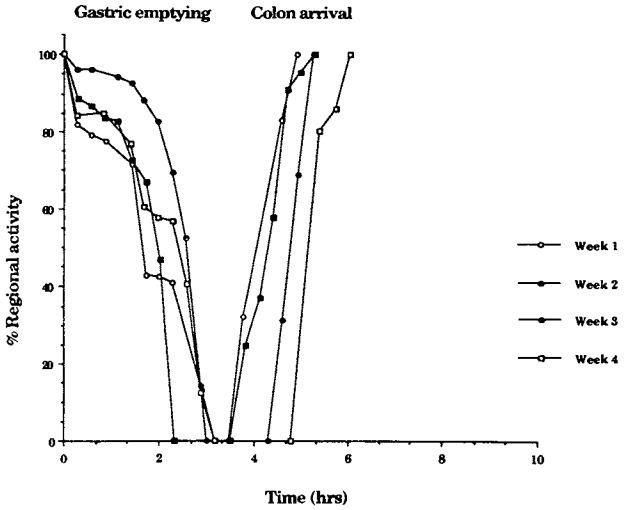

Fig. 2. Total transit profiles for volunteer 5.

system was observed to stagnate at the ileocecal junction before passage into the colon; however, no apparent trend was noted.

Influence of Conditioning on Transit

The mean gastric emptying times (Tables II and IV) and small intestinal transit times (Tables III and V) were calculated for each week to investigate the possibility of conditioning or adaptive response on the study days. The results show little variation and it is assumed that there is no contrived variation between any of the study days.

DISCUSSION

Gastric Emptying

The manner in which the stomach handles dosage forms is dependent primarily upon the dietary state of the stomach (fed or fasted) and the size of the dosage form. It has been postulated that liquids and small particulates are emptied from the fed stomach, whereas solids are retained for reduction to a size suitable for passage into the duodenum (16). Digestible solids are ground and triturated into small particles and empty with the liquid phase of the meal, whereas large indigestible solids are retained in the fed stomach and are emptied only by contractions associated with the migrating myolectric complex (MMC) of the fasted stomach. The contractive waves of the MMC have been termed the "interdigestive housekeeper" of the gastrointestinal tract (17). Consequently, the results would be expected to show that the large single-unit tablet was retained in the stomach until the indigestible fasting contents are emptied by the housekeeper wave. However, it was observed that the tablet was emptied in the majority of cases before all the pellets had emptied. Two theories have been postulated to explain this phenomenon. First, the pellets upon dispersion in the stomach may become lodged within the folds of the stomach wall, thus prolonging their residence time. Second, contractions of the stomach in the digestive mode can cause a large object to be emptied fortuitously. A similar phenomenon has been noted previously (18), following administration of two large single-unit dosage forms (12-mm diameter). It was observed that in some subjects the tablets did not empty concurrently, and in one case, one of the tablets was retained in the stomach for 100 min after the other had entered the small intestine. In addition, the results of the present study suggest that the 2-mm cutoff size for gastric emptying, proposed by Hinder and Kelly, from canine studies (16) is not applicable to man. Our findings agree with recently published data (19) which found no difference in the gastric emptying of 5-, 6-, and 7-mm tablets. Smith and Feldman (20) also failed to demonstrate a significant difference between the gastric emptying of 2-mm and that of 10-mm radioopaque markers from the fed human stomach. It is thought that the results can be attributed to random/fortuitous emptying and the diameter of the resting pylorus. Khosla *et al.* (19) have suggested that gastric emptying becomes less predictable as the size of the dosage form increases up to a cutoff point which will vary between subjects. The cutoff size was thought to be related to the mean resting pyloric diameter [in man, 12.8 ± 7 mm (21)]. Nondisintegrating systems of a size in excess of the mean diameter of the pylorus have been shown to be retained in the stomach for as long as the digestive phase is maintained (15).

The magnitude of variation is similar to that published by Brophy *et al.* (9) and shows that variation in gastric emptying is large for both multiple- and single-unit dosage forms, the greater variation being observed with the single-unit system. It is known that gastric emptying is influenced by various factors including the presence or absence of food (14), nature of the controlled-release dosage form (14), exercise (22), stress (7), and body posture (23). The study protocol was designed to eliminate or, at best, reduce the factors known to affect gastric emptying so that natural variation could be assessed. It is thought that the phenomenon of random/fortuitous emptying may be a contributory factor to the large variation in gastric emptying of single-unit systems and that gastric emptying becomes less predictable as tablet diameter increases.

Small Intestinal Transit

The average small intestinal transit time of pharmaceutical dosage forms has been given as 180 min (SD, ±60 min) (14) and is apparently unaffected by exercise (24), physical form (14), or whether the subject has been fed (3,14). The results from our investigation (Tables III and V) are in excellent agreement with this proposal; the mean small intestinal transit time for the single-unit dosage form was 182 min (±69 min) and that for the multiple-unit dosage form was 209 min (±60 min). The coefficients of variation for small intestinal transit times are less than those for gastric emptying. This result is not surprising due to the fact that small intestinal transit is affected by fewer physiological factors than is gastric emptying. The variation in small intestinal transit for single-unit and multiple-unit systems is also comparable, providing further evidence that transit through the small intestine is independent of the nature of the dosage form. In some cases small intestinal transit times are of the order of 180 min; however, the dosage form is help up at the ileocecal junction for an indeterminable period of time before entering the cecum, leading to extended transit times. This phenomenon of stagnation in the ileocecal region has been reported previously (19) and warrants further investigation.

CONCLUSIONS

The results demonstrate that the gastrointestinal transit of both multiple-unit and single-unit dosage forms exhibits relatively wide inter- and intrasubject variation. These results are not totally unexpected due to the many factors which are known to influence transit of material through the gastrointestinal tract. The finding of relatively wide inter- and intrasubject differences emphasizes the importance of appropriate scintigraphic studies on new delivery systems so that information can be gained on their *in vivo* behavior. Moreover, when interpreting the results of an individual study, it is important to be aware of the intrasubject variation that can occur, and conclusions on *in vivo* results should be drawn only from studies where clear-cut differences are observed.

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