Correlation of the Gastric Emptying of Nondisintegrating Tablets with Gastrointestinal Motility

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Received October 24, 1990; accepted April 16, 1991

The aim of the present study was to correlate the gastric emptying (GE) of nondisintegrating tablets with changes in gastrointestinal (GI) motility. Eight, healthy, male subjects each received 5 × 7-mm radiolabeled tablets, a radiolabeled meal, and a radiotelemetry capsule (RTC). Transit of the radiolabeled formulations was followed by gamma scintigraphy and the RTC detected contractile activity in the GI tract. The study demonstrated that 7-mm tablets can empty from the fed stomach, prior to the onset of interdigestive activity. Those tablets that were not emptied during fed activity were retained through the period of quiescence associated with the onset of the migrating myoelectric complex (MMC) and left the stomach during contractions associated with phase 2 and 3 activity. The RTC was retained in the stomach and was emptied only by large phase 3 contractions commonly termed the "housekeeper" wave. However, in one subject, the RTC was retained in the stomach for over 12 hr, during which time three distinct phase 3 complexes were monitored.

KEY WORDS: gamma scintigraphy; radiotelemetry, gastric emptying; pharmaceutical dosage forms.

INTRODUCTION

Many studies have been conducted to investigate the factors affecting the gastrointestinal (GI) transit of oral dosage forms (1,2). Much attention has been paid to gastric emptying (GE), in particular the relationship between GE and particle size (3,4). It has been suggested that postprandial GE of nondisintegrating tablets does not occur until the fed activity of the stomach is replaced by that of the fasted state. However, recent studies (5) have shown that tablets as large as 11-mm can leave the fed stomach. This is in marked contrast to the much quoted 2-mm cutoff point suggested from canine studies by Kelly (6), who indicated that particles greater than 2 mm in diameter were not emptied from the fed stomach but were retained and emptied with the powerful phase 3 contractions of the migrating myoelectric complex (MMC) (7). Further studies in dogs (8) have suggested that there was no cutoff point per se but a gradation of size over which the stomach allows particles to empty. Smith and Feldman (9) showed no significant difference in the emptying of markers, 2 and 10 mm in length, of constant 2-mm diameter, from the fed stomach in man and concluded that GE of indigestible solids in humans is not influenced by the length of the particles used. Similar results were obtained by Khosla *et al.* (3), investigating the GI transit of 3-, 4-, 5-, 6-, and 7-mm nondisintegrating tablets. Khosla *et al.* (4) further investigated the GE of 7-, 11-, and 13-mm tablets from the fed stomach and showed GE times of less than 1 hr for 7-mm tablets in two of five subjects, suggesting that large tablets can empty from the fed stomach. However, the study protocol did not permit the authors to assess whether the tablets emptied during the digestive phase or whether emptying occurred during one of the phases of the interdigestive activity, since it was difficult to determine when the fed state ended and the activity of the MMC began. The present study was designed to overcome this problem by the coadministration of a radiolabeled meal. Further evidence of GI motility was provided by the administration of a pressure-sensitive radiotelemetry capsule (RTC). RTCs provide a noninvasive method for the measurement of GI motility which is comparable to other techniques for the evaluation of motility (10). Due to their size (25 × 8 mm) the RTCs permit an assessment to be made of large particulate GE. The aim of this study was to relate the GI transit of nondisintegrating tablets to GI motility.

MATERIALS AND METHODS

Radiolabeling of Formulations

Nondisintegrating tablets (7-mm diameter, 140-mg weight) were prepared from ethylcellulose (BDH, Poole, Dorset) containing a small quantity (5%) of ^{111}In-labeled amberlite IR-120 cationic resin (BDH, Poole, Dorset). The tablets were directly compressed using 7-mm round, shallow concave punches to give a total activity of 1 MBq at the time of administration. The tablets were dual coated with ethylcellulose and cellulose acetate to prevent leaching of the radiolabel and *in vivo* disintegration. A more detailed description of tablet preparation can be found elsewhere (5).

Radiolabeled eggs on toast were prepared by the method described previously by Knight and Malmud (11) using ^{99m}Tc sulfur colloid to give an activity of 3 MBq at the time of administration.

Telemetry

GI motility was monitored using a pressure-sensitive RTC (Remote Control Systems, London). The RTC measured 25 × 8 mm with a battery life of 90 hr. The RTC was radiolabeled (1 MBq ^{99m}Tc as a sealed source placed in the battery compartment) and was enclosed within a rubber sheath to protect the pressure-sensitive diaphragm from fecal material. The RTC was allowed to stabilize for 12 hr at 37°C and was then calibrated before ingestion (12). After administration, signals transmitted from the RTC are detected by an aerial worn around the subject's waist. The radio signal was processed and amplified and then recorded onto a chart recorder.

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0724-8741/91/1000-1281$06.50/0

Table I. Gastric Emptying Time of RTC (Hours)

Subject No.	Scintigraphy	Telemetry
1	4.33	4.32
2	4.33	4.40
3	7.05	7.18
4	4.80	4.83
5	>12	>12
6	1.98	1.80
7	4.50	4.30
8	3.50	3.25

Study Design

The study 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, London.

Eight, healthy, male volunteers, age 19–24 years, provided written informed consent to participate. Each subject abstained from alcohol for 24 hr, did not smoke, and was not receiving any medication. Following an overnight fast each subject received breakfast consisting of one radiolabeled scrambled egg on a piece of toast and a cup of tea (1200 kJ) which was consumed over a 5-min period. Labeled tablets (5 × 7 mm), the RTC, and 100 ml of water were taken immediately after breakfast. Lunch was not taken until all the radiolabeled contents had left the stomach and fluids were also restricted until the stomach was empty of all its radioactive contents. Anterior and posterior images, each of 60-sec duration, were taken at frequent intervals immediately after dosing, using a gamma camera (General Electric Maxicamera, Type II) having a 40-cm field of view and fitted with a medium-energy (300-keV maximum energy) parallel-hole collimator. The images were recorded using a Nodecrest computer system and stored on magnetic tape for subsequent analysis.

Data Analysis

The recorded scintigraphic images were analyzed by drawing regions of interest around the stomach, and the activity in these regions was quantified as described previously (13). Motility measurements were recorded continuously throughout the study period. Each trace was analysed manually by an investigator who was without prior knowledge of the scintigraphic data. At the end of the study the RTC was passed per rectum and recovered.

Table II. Gastric Emptying Times of Radiolabeled Food (Hours)

Subject No.	Scintigraphy	Telemetry
1	1.50	2.00
2	3.00	2.65
3	2.75	2.95
4	2.50	2.58
5	2.50	2.43
6	1.25	0.50
7	1.50	3.20
8	1.50	1.83

Table III. Gastric Emptying Time of 5 × 7-mm Tablets (Hours)

Subject No.	Tablet No. 1	2	3	4	5
1	3.27	3.43	3.75	4.07	4.07
2	1.80	1.80	2.07	2.23	4.20
3	1.38	1.68	1.95	2.23	2.57
4	0.70	1.13	1.22	1.68	4.80
5	0.33	3.42	3.42	3.52	3.62
6	0.08	0.08	0.18	0.18	0.27
7	0.08	0.08	0.08	0.08	0.87
8	0.20	0.38	0.38	0.52	0.63

RESULTS

The tablets passed from mouth to anus intact in all volunteers in accord with previous studies (3–5), thereby confirming *in vivo* integrity.

By examining the traces it was possible to determine the position of the RTC within the GI tract, in particular the GE of the device (Table I). Table I also contains data for the GE of the RTC as assessed by scintigraphy. The motility traces also permit an assessment to be made of when the fed activity ceased and this is reported along with the scintigraphic GE times for the radiolabeled meal in Table II. GE times for the nondisintegrating tablets as assessed by scintigraphy are represented in Table III. Figures 1–8 represent graphically the GE profiles of the radiolabeled meal. Superimposed on the graphs are the GE times for the individual tablets and the RTC as assessed by scintigraphy and, also, the duration of the fed state as assessed by telemetry. Phase 3 activity was signified by a short burst of high-amplitude contractions, typically 3 contractions/min, preceded by intermittent medium-high amplitude contractions.

DISCUSSION

Gastric motility can be divided into two distinct modes: fed and fasted activity (14). The interdigestive period is characterized by a distinct cycle of motility (15). This cycle is termed the MMC, which recurs approximately every 2 hr

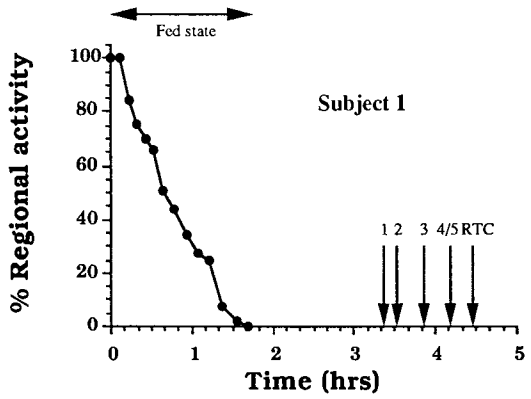

Fig. 1. Gastric emptying profile for subject 1.

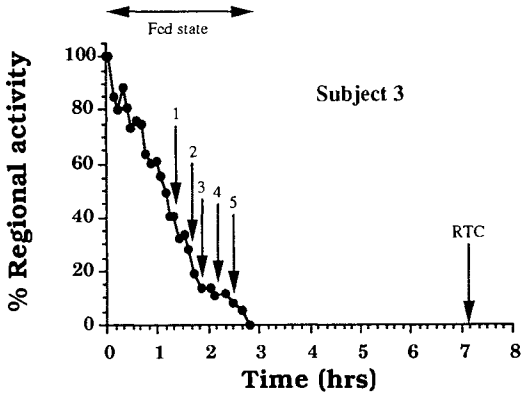

Fig. 2. Gastric emptying profile for subject 3.

and exhibits four distinct phases:

phase 1, quiescence (30–60 min);
phase 2, irregular or random medium-high-amplitude contractions (20–40 min);
phase 3, high-amplitude phasic contractions at the maximal frequency (5–15 min); and
phase 4, decreasing contractions merging into phase 1 (0–5 min).

Upon feeding, the motility of the stomach returns to frequent contractions of an amplitude lower than those observed during phase 3. The disruption of the MMC lasts for as long as the food is present in the stomach. It has been suggested that the peristaltic waves of the stomach cause digestible solid food to be ground down to a size suitable for passage into the duodenum with the fluid portion of the meal (6). Larger indigestible solids are retained and are emptied only by the phase 3 contractive waves of the MMC, termed the "interdigestive housekeeper wave" (7).

The aim of the present study was to correlate the GE of nondisintegrating tablets with these motility patterns. In all subjects the characteristic motility patterns were observed, as described earlier. However, the emptying of the tablets in relation to the motility activity did not show just one trend and several patterns were exhibited (Figs. 1–8).

Subject 1 exhibited the classical emptying pattern for

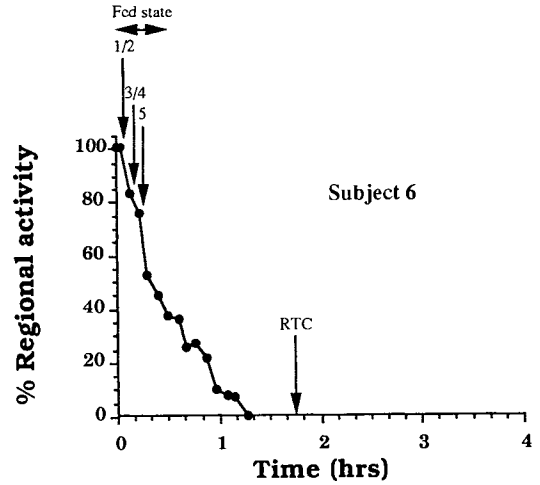

Fig. 3. Gastric emptying profile for subject 6.

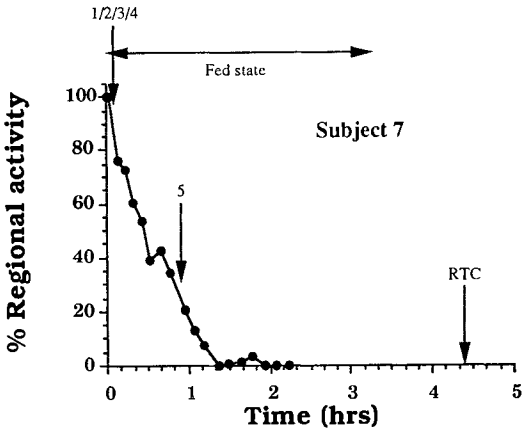

Fig. 4. Gastric emptying profile for subject 7.

indigestible material, as illustrated in Fig. 1. The GE time for the radiolabeled meal was 1.5 hr, and during this time no tablets emptied the stomach. This is in accord with previous results that particles larger than 2-mm in size (6) do not empty the fed stomach. Following the digestive state a period of quiescence (phase 1) was observed in which no tablets left the stomach. The tablets then emptied during the phase 2 contractions and the RTC emptied with the phase 3 contractions 3 hr after the onset of the MMC.

For subjects 3, 6, 7, and 8 (Figures 2, 3, 4, and 5, respectively) all the tablets left the stomach during fed activity, a period of quiescence followed, and the RTC emptied on waves associated with phase 3 activity. These results are at a variance to the much quoted 2-mm cutoff size. It has been postulated (3) that tablets become trapped in the terminal antrum and that on the next contraction the tablet is forced through the partially occluded pylorus. A GE time of over 7 hr was observed for the RTC in subject 3, despite phase 3 activity being noted at 5.5 hr. It is suggested that the RTC remained in the less muscular body of the stomach and was not propelled into the antrum of the stomach where emptying could take place. This phenomenon of extended gastric residence has been seen previously with large single-unit devices (16).

Figures 6 and 7 (subjects 2 and 4) illustrate the emptying of a number of the tablets during the fed state, in each case 4 tablets. Following the emptying of food a period of quies-

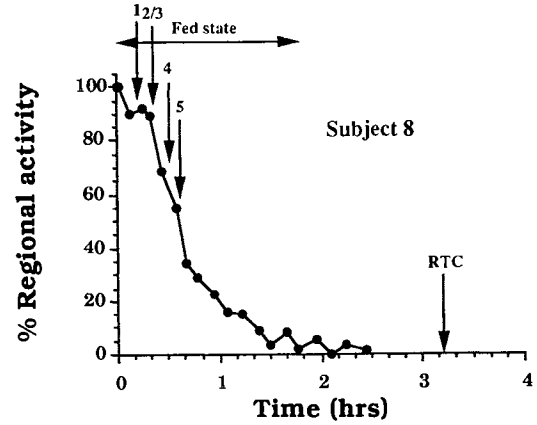

Fig. 5. Gastric emptying profile for subject 8.

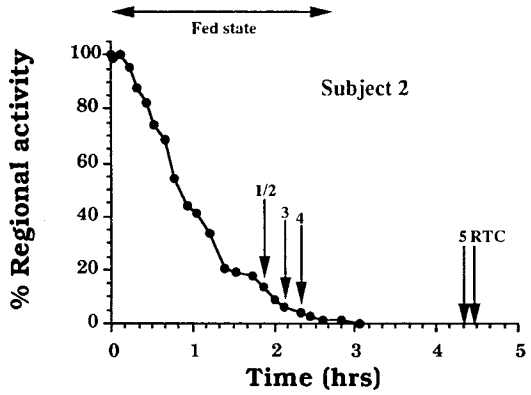

Fig. 6. Gastric emptying profile for subject 2.

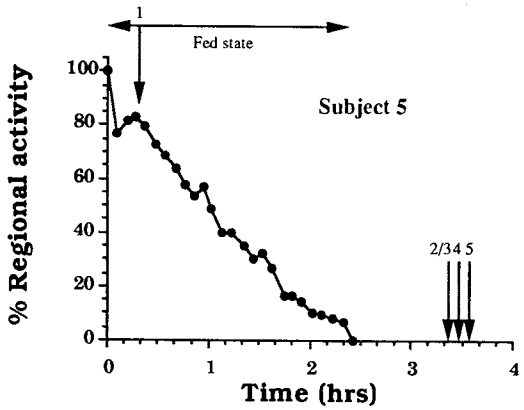

Fig. 8. Gastric emptying profile for subject 5.

cence was observed and the final tablet and the RTC emptied the stomach with the phase 3 contractions. A similar result was observed with subject 5 (Fig. 8), in whom one tablet emptied while the stomach was in the fed state, the remainder leaving with the phase 2 and 3 contractile waves. However, the RTC did not leave the stomach of subject 5 within 12 hr postadministration, even though phase 3 contractions were noted at 4.5, 6.5, and 8.5 hr postdose. The GE time of the radiolabeled meal, for this subject, was 2.5 hr, therefore indicating a 2-hourly recurring MMC. This again shows that the phase 3 contractions of the MMC are not always efficient at removing large nondisintegrating dosage forms from the stomach.

In no subject was the RTC seen to empty from the stomach while it was in the fed state, suggesting that the size of the RTC is above that of the critical value for GE while in the digestive state. A critical value similar in diameter to the aperture of the resting pylorus, 12.8 ± 7 mm (17), has been suggested (4).

CONCLUSIONS

The results show that the contractions of the fed stomach are sufficiently strong to empty the tablets of the size used in this study (7-mm) but not the RTC. The medium-high contractile waves of the fed stomach result in the random/fortuitous emptying, as described by Khosla *et al.* (3). If the tablets are not emptied during the digestive phase they are retained in the stomach through phase 1 of the MMC and empty with medium-high contractile waves associated with phase 2 of the MMC. Large phase 3 contractions follow phase 2 and are usually sufficient to empty the stomach of all its undigested contents including the RTC. However, it has been shown in this study that this is not always the case and the RTC can be retained in the stomach for longer than 12 hr, resisting emptying by the phase 3 contractions.

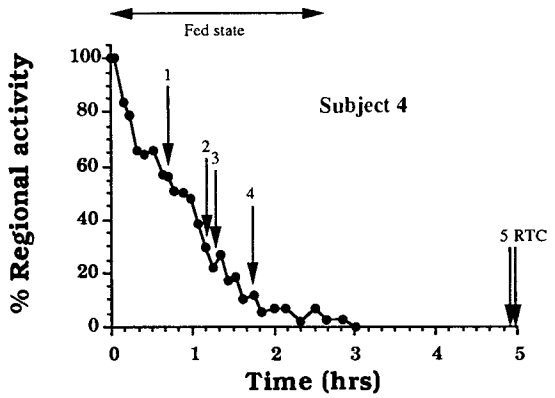

Fig. 7. Gastric emptying profile for subject 4.

ACKNOWLEDGMENT

The authors wish to thank the Science and Engineering Research Council for financial assistance to A.J.C.

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