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Research Article

The Effect of Density on the Gastric Emptying of Single- and Multiple-Unit Dosage Forms

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The gastric emptying of pellets and single units of different densities has been followed in healthy subjects using the technique of gamma scintigraphy. The gastric emptying of the light pellets was affected by their buoyancy in the upper part of the stomach. However, the mean gastric emptying rates of pellets and single units were not significantly affected by density. Floating or buoyant delivery systems may have little advantage over conventional systems. The presence of food in the stomach was found to be the major factor in determining the gastric emptying of single units.

KEY WORDS: gastrointestinal transit; pellet density; floating formulations, gastric emptying.

INTRODUCTION

The biological availability of a drug can be affected by the transit of an orally administered dosage form within different regions of the gastrointestinal tract, particularly for the case of controlled-release dosage forms (1). Some drugs are well absorbed from all regions of the intestines, while others are poorly absorbed from the colon or have so-called "windows for absorption" within the small intestine (2). Increased, or more predictable, biological availability might result if controlled-release systems could be retained in the stomach for extended periods of time.

Gastric emptying is known to be influenced by a variety of physiological factors, including dietary intake and exercise, as well as disease conditions and stress (3). Dosage forms administered to a fasted or lightly fed subject will empty quite rapidly, while single units will be retained in the stomach following a large meal for much longer periods of time (4). Various attempts have been made to control gastric emptying through pharmaceutical means. The literature contains examples of systems that have been designed to swell to a size too large to pass through the pyloric sphincter (5), as well as adhesive systems that would "stick" dosage forms to the gastric mucosa (6). Another suggestion has been the floating capsule that could remain in the upper part of the stomach, thereby delaying its transit (7). A commercial product, Valrelease, that exploits this last concept has been marketed by Roche.

Bechgaard and Ladefoged (8) attempted to alter the gastrointestinal transit of pellets and tablets through the use of density. For ileostomy subjects they reported that the average transit times for light and heavy pellets (densities, 1.0 and 1.6 g cm^{-3}, respectively) from mouth to ileostomy bag were 7 and 25 hr, respectively. However, in more recent studies, conducted in normal individuals as well as ileostomy subjects, such differences in transit have not been confirmed (9,10).

The objective of the present study was to determine the influence of density on the gastric emptying of pellets and single units from the stomach of normal volunteers to assess the advantages, if any, of floating tablet and pellet systems over conventional nonfloating systems. The preparations were monitored using gamma scintigraphy, and the use of two radionuclides permitted crossover studies to be performed on a single occasion (light versus heavy pellets, floating capsule versus floating tablet, and floating capsule versus nonfloating tablet).

MATERIALS AND METHODS

Single Units

Nonfloating Unit. Nondisintegrating tablets of nominal weight 400 mg and density approximately 1.20 g cm^{-3} were prepared using ethylcellulose (BDH Chemicals, Poole) and 12 mg Amberlite IRA410 resin (BDH Chemicals, Poole) labeled with technetium-99m (approximately 2 MBq per tablet). The tablets were compressed using 10-mm-diameter flat-faced punches at a compaction pressure of 150 MNm^{-2}.

Floating Unit. Floating matrix tablets of nominal weight 300 mg containing hydroxypropylmethylcellulose (Methocel K100M) (Colorcon, Orpington) and 50 mg of Amberlite IRA410 resin (BDH Chemicals, Poole) labeled with

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technetium-99m (approximately 2 MBq per tablet) were compressed as for the nonfloating units. The tablets had a density of approximately 1.25 g cm^{-3} but floated after 15 min under *in vitro* and *in vivo* conditions following the formation of a gel layer at the surface of the tablet.

Floating capsule systems were made by filling size 1 hard gelatin capsules with a mixture of sodium alginate and sodium bicarbonate as described previously (11). These systems had been shown to float in *in vitro* tests through the generation of carbon dioxide that was trapped in the hydrating gel network when in an acid environment. Each capsule of nominal weight 450 mg contained 50 mg of Amberlite IR120 resin labeled with indium-113m (approximately 3 MBq per capsule). The drug–capsule system had a density of 0.63 g cm^{-2}.

Pellets

Nontoxic light pellets of 0.94 g cm^{-3} (sieve fraction, 0.7–1.0 mm) were prepared from hard paraffin and labeled with technetium-99m using sodium pertechnetate obtained by elution from a generator. Nontoxic heavy pellets of density 1.96 g cm^{-3} (sieve fraction, 0.7–1.0 mm) were prepared using barium sulfate and were labeled with indium-111 using carrier-free ^{111}In-indium chloride solution in 0.04 *M* HCl (Amersham International, Amersham) (10).

In Vivo Studies

Twelve healthy male subjects (age, 19–23 years; height, 1.77–1.85 m; weight, 64–73 kg) participated after giving informed consent. The study was approved by the Ethical Committee of Nottingham University. Four took the pellet system and eight took the single units. For the pellet study each subject had a light breakfast, comprising cereal, coffee or tea, toast, butter, and marmalade, at least 1 hr before the concurrent administration of the two pellet systems. The individual pellet suspensions were dispersed in a standard mixture of Complan (100 g) (dietetic food for weight reduction) in 300 ml of water. Approximately 500 pellets of each type were given.

For the studies on single units four subjects received the two different floating systems (tablet and capsule) concurrently, while a second group of four subjects received the nonfloating tablet and floating capsule together. The subjects were given both dosage forms according to a crossover design in order to follow the effect of food. On one occasion the dosage forms were administered after an overnight fast, and on another occasion following the light breakfast described above. The two parts of the studies were conducted 1 week apart.

Simultaneous imaging of two radionuclides was undertaken with the subjects standing, using a gamma camera having a field of view of 40 cm diameter fitted with a medium-energy (300-keV-maximum) or high-energy (400-keV maximum) parallel hole collimator as appropriate. External anatomical reference markers made from adhesive tape labeled with a small quantity of technetium-99m were positioned anteriorly and posteriorly over the liver to the right of the stomach. Anterior and posterior images of 60-sec duration were taken at suitable intervals over periods of up to 24 hr. The data were recorded on a computer for analysis later. For the pellet systems a region of interest was defined around the stomach and the count rate from this region was determined and corrections were made for background count rates. When undertaking imaging using two radionuclides a correction sometimes needs to be made for the "scatter down" of the activity of a higher-energy radiation (e.g., from indium-111) into the energy window of a lower-energy photopeak of technetium-99m. A correction factor was obtained by administering the indium-111-labeled pellets before the technetium-99m-labeled pellets and imaging on both energy channels for indium-111 alone. The counts were then corrected for radioactive decay and a geometric mean of the anterior and posterior counts was taken to give a result for activity that was approximately independent of the depth of the source (12).

The subjects were allowed to drink and eat normally during the course of the study and a light lunch was taken about 3 hr after dosing. The subjects taking the single units were given a drink of water (250 ml) containing 0.5 MBq ^{99m}Tc-labeled diethylenetriaminepentaacetic acids (CIS, U.K.) in order to outline the stomach.

RESULTS AND DISCUSSION

Single Units

Gastric emptying times for the floating and nonfloating systems for fasted and fed states are given in Table I. Since the emptying of single units is an all-or-nothing process, the times given are estimates obtained from consecutive views. Representative images are shown in Figs. 1–4. The gastric emptying of the single units was generally much faster when administered to an empty stomach than when they were given after a light breakfast. For the fasted state the various systems were usually emptied in less than 2 hr and in some cases emptying occurred within the first half-hour. There were no significant differences in emptying time that could be attributed to the nature of the floating and nonfloating systems for the sample size examined ($N = 4$).

The images obtained for fasted subjects show the floating of the HPMC matrix tablet and alginate capsule immediately after administration and the emptying of the tablet at 1 hr (Fig. 1). The capsule emptied at about 1.5 hr. In contrast in Fig. 2 the sinking of the ethylcellulose tablet and the floating of the alginate capsule immediately and 1 hr after administration may be noted. Interestingly, for one subject (No. 5) there was no difference in the times for gastric emptying (120 and 135 min, respectively) even though floating of the capsule had occurred.

The rapid emptying of single units from a fasted stomach is in accord with previous investigations on gastric emptying and known gastrointestinal physiology (2,4). Under fasting conditions gastrointestinal motility is characterized by periods of strong motor activity [the migrating myoelectric complex (MMC)] which occur approximately every 1.5–2 hr, separated by quiescent activity (13,14). The MMC will "sweep" undigested material from the stomach and through the small intestines. Thus a dosage form will leave a fasted stomach erratically and unpredictably according to the timing of a MMC (15). If the administration of the units coincides with the occurrence of such activity, then the units could be expected to empty rapidly. Dosage forms

Table I. Gastric Emptying of Single Units: Approximate Times for Transfer (min)

Subject No.	Floating systems				Nonfloating tablet	
	Tablet		Capsule			
	Fasted	Fed	Fasted	Fed	Fasted	Fed
1	75	240	90	240		
2	15	>420	30	180		
3	60	180	90	180		
4	45	>420	30	>420		
Mean	49	>315	60	>255		
SE	13	>62	17	>57		
5			135	>420	120	45
6			>420	>420	100	>420
7			180	>420	75	180
8			75	>420	100	>420
Mean			>202	>420	99	>266
SE			>75.6	—	9.2	92.9

administered concurrently usually empty together, although in some cases (e.g., subjects 6 and 7) the floating capsule was able to remain in the stomach after the nonfloating tablet had emptied. It should be noted that a liquid will empty from the stomach according to a first-order process and is characterized by a half-time of about 30–50 min (16). Thus, after about 2 hr there will be little fluid within the stomach on which the unit can float.

The activity of the MMC ceases as soon as food is given and reappears about 2–3 hr after the meal has emptied. Consequently if a single unit fails to be cleared from a fasted stomach by the MMC before the first meal (lunch), it will then have an extended period within the stomach (see, for example, subject 6, where in the original fasted state the time for gastric emptying was greater than 420 min).

A single unit will normally be unable to empty from a fed stomach since the pylorus is effective in sieving the gastric contents and retaining solid particles (17). Therefore, following a light breakfast the various single units will have to await the emptying of the digested meal and the occurrence of a MMC. The process is not always totally effective. In the fed state it is quite likely that a further meal will be

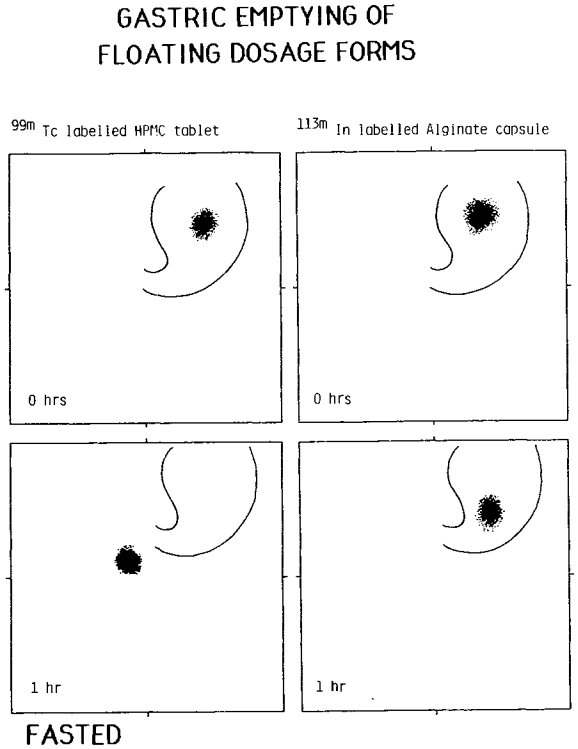

Fig. 1. Radionuclide images obtained after simultaneous administration of floating tablet (HPMC) and floating capsule (alginate) to fasted subject (Subject 3).

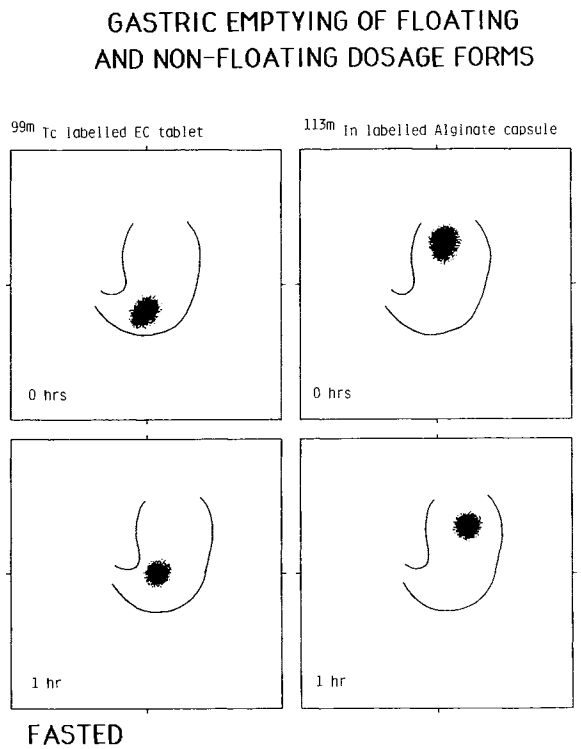

Fig. 2. Radionuclide images obtained after simultaneous administration of nonfloating tablet (ethylcellulose) and floating capsule (alginate) to fasted subject (Subject 5).

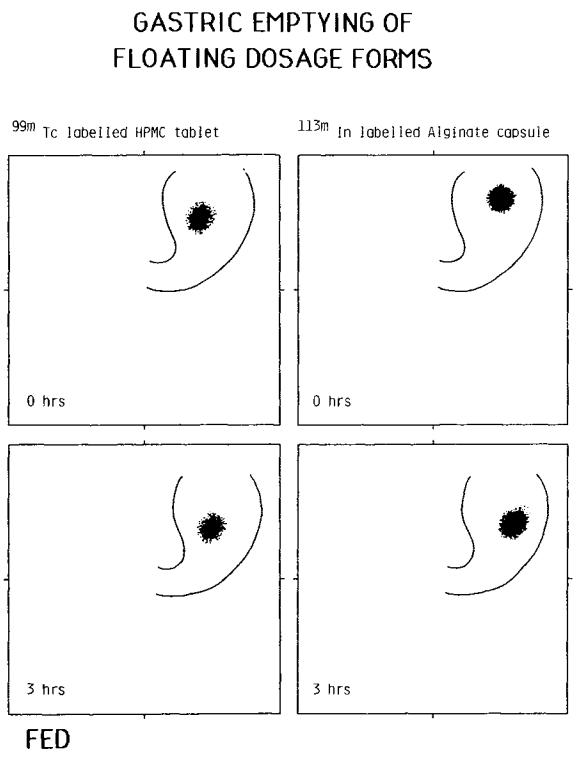

Fig. 3. Radionuclide images obtained after simultaneous administration of floating tablet (HPMC) and floating capsule (alginate) to fed subject (Subject 3).

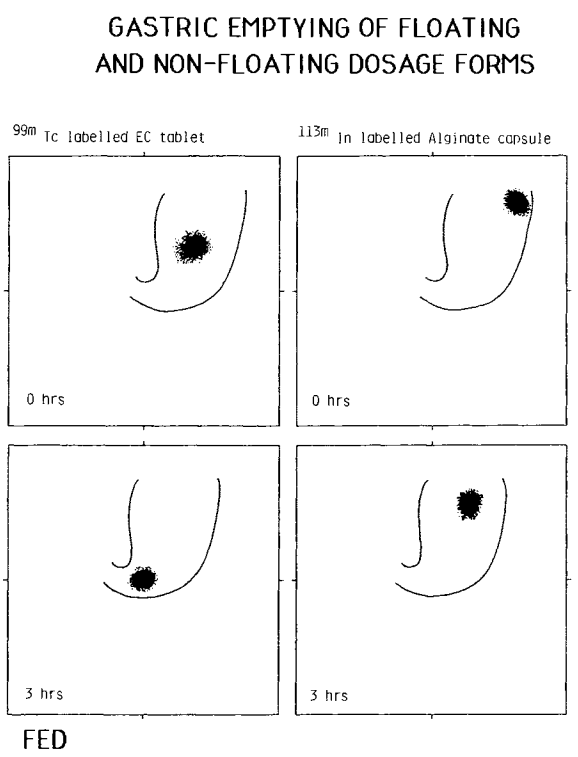

Fig. 4. Radionuclide images obtained after simultaneous administration of nonfloating tablet (ethylcellulose) and floating capsule (alginate) to fed subject (Subject 5).

taken before the arrival of the first MMC, with the result that single units can remain in the stomach over extended periods of time (10 hr or longer), depending on the frequency and quantity of food intake (18).

The radionuclide images shown in Figs. 3 and 4 show the floating of the HPMC tablet and alginate capsule at 3 hr and the presence of the nonfloating tablet in the antrum of the stomach at the same time period (Fig. 4). While floating can be achieved its advantage in controlling gastric emptying is not apparent. For gastric emptying the size of the dosage form and its nondigestibility would seem to be more important factors than any ability to float. However, the data in Table I do suggest the possibility that a floating system could be more reliable in providing a delayed emptying pattern from a stomach containing food. Certainly the dosage form should have less chance of "fortuitous empting" from a full stomach.

The present results are in agreement with those of Müller-Lissner and Blum (7), who found food intake to be the main influence on the gastric emptying of floating and nonfloating capsules, with density having only a minor effect. Previous *in vivo* evaluations of floating drug delivery systems by Müller-Lissner *et al.* (19) and Sheth and Tossounian (20) have reported gastric residence times of 4–10 and up to 6 hr, respectively, the former after a fat and protein test meal. The present data support these figures but it is believed that density has a minor role in controlling gastric emptying as compared to diet and there is little advantage to be gained by formulating complex systems that will float in the stomach.

Pellets

The gastric emptying profiles obtained for each of the four subjects are shown in Fig. 5 and the mean and SE values are given in Fig. 6. In two subjects the emptying profiles for the light and heavy pellets show somewhat different

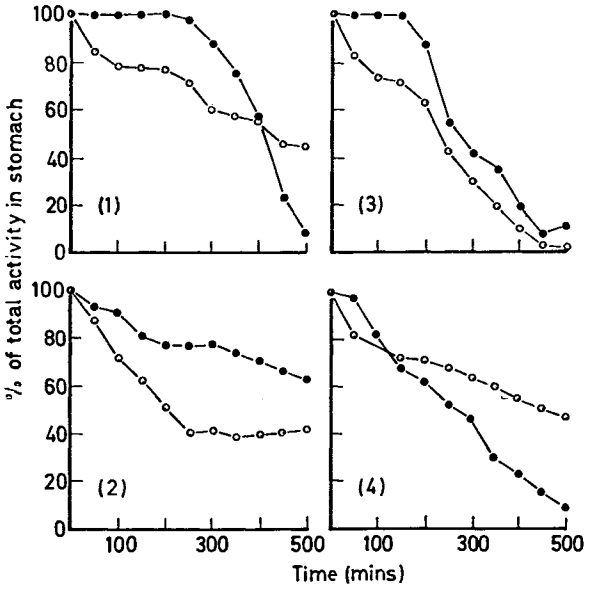

Fig. 5. Individual gastric emptying profiles for pellets for four subjects. (●) Light pellets; (○) heavy pellets.

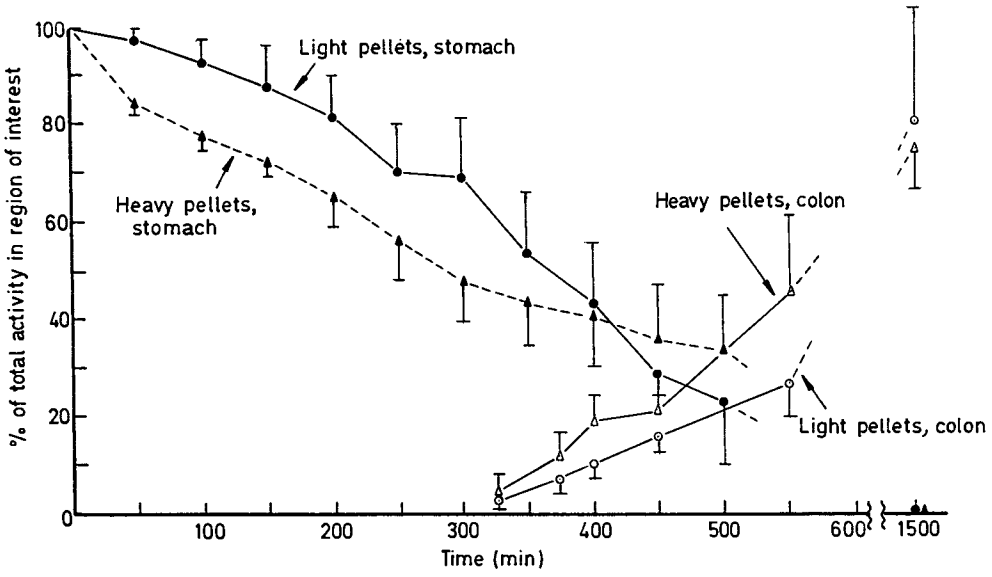

Fig. 6. Gastric emptying of light and heavy pellets in normal subjects (mean ± SE; $N = 4$).

patterns; the emptying of the heavy pellets conforms quite well to a single linear function, whereas the light pellets show a two-phase pattern. Furthermore, at early times the rate of emptying of the heavy pellets is greater than that for the light pellets, which tended to float toward the fundus of the stomach (Fig. 7). At later times the light pellets ceased floating and then generally were emptied more quickly from the stomach than the heavy pellets. The times for emptying 50% of the light and heavy pellets are given in Table II. There is no significant difference ($P > 0.1$) between the derived data for light and those for heavy pellets.

These results for the pellet systems showing no significant effect on gastric emptying attributable to density are in agreement with studies by Bogentoft *et al.* (9) conducted in normal subjects and those reported more recently by Bechgaard *et al.* (10) using ileostomy subjects. The present study indicates that light pellets are able sometimes to undergo a different pattern of gastric emptying than heavy pellets. The former demonstrate a distinct floating phase in subjects, while the latter tend to deposit at the lowest point of the greater curvature of the stomach. However, when the derived data were expressed in terms of time for 50% emptying, there was no difference to be found. This is because once the light pellets start to empty when the fluid level in the stomach decreases, they appear to do so more quickly than the heavy pellets, with the result that the two emptying profiles can intersect.

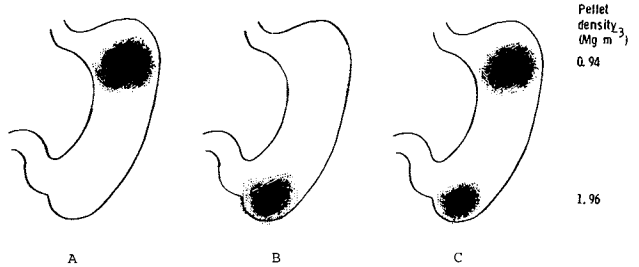

Fig. 7. Scintigraphic images demonstrating the floating of the light pellets in the stomach, soon after administration. (A) Technetium-99m-labeled preparation; (B) indium-111-labeled preparation; (C) combined image.

Table II. Gastric Emptying of Pellets: Time for 50% Emptying (min)

Subject No.	Pellets	
	Heavy	Light
9	432	410
10	200	450
11	240	270
12	425	280
Mean	325	353
SE	61	61

CONCLUSIONS

The use of density as a means of altering the gastric residence time of pharmaceutical dosage forms (multiple and single units) has little or no value. The major factor determining the gastric emptying of single units is the presence of food.

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