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Do pellet formulations empty from the stomach with food?

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Summary

The aim of the present study was to correlate the gastric emptying (GE) of a pellet formulation with changes in gastrointestinal (GI) motility. Eight, healthy, male subjects each received one capsule containing radiolabelled pellets, a radiolabelled meal and a radiotelemetry capsule (RTC). Transit of the radiolabelled formulations was followed by gamma scintigraphy. The RTC is used to detect contractile activity in the GI tract. GE of the pellet formulation did not follow any particular trend. In two of the eight subjects, the radiolabelled meal and the pellet formulation emptied from the stomach at similar rates, however, in the other six subjects the pellet formulation emptied from the stomach slower than the coadministered radiolabelled meal. The possible reasons for the delayed emptying of the pellet formulation are discussed.

Introduction

Oral controlled release (CR) dosage forms may be conveniently divided into two types, the single-unit (SU) dosage form which is typically a nondisintegrating depot releasing drug during passage of the entire gastrointestinal (GI) tract and the multiple-unit (MU) dosage form which disintegrates in the stomach to give a large number of CR subunits (Bechgaard and Nielsen, 1978). The in vivo behaviour of the two types of delivery system has been studied extensively over recent years and has been shown to differ markedly (Davis et al., 1984; Marvola et al., 1989). It has been suggested that dosage forms empty from the stomach as a function of their size, a sieving mechanism being present which influences gastric emptying (GE) (Gupta and Robinson, 1992). In general, dosage forms greater than 2 mm in diameter are retained within the stomach during the postprandial phase and empty once fed activity is replaced by that of fasted activity. However, recent studies have shown that large SU dosage forms can empty from the fed stomach (Khosla et al., 1989; Khosla and Davis, 1990) and that the 2 mm cut-off size, quoted from canine data, may not be applicable to man. The mechanisms of GE of SU dosage forms has been studied by concomitantly measuring GI motility

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by pressure sensitive radiotelemetry and GI transit by gamma scintigraphy (Coupe et al., 1991a). It has been demonstrated that 7 mm tablets can empty from the fed stomach and that those tablets which resist the fed state contractile activity are retained throughout the early fasted activity and are emptied from the stomach by contractions associated with phase 2 and phase 3 of the interdigestive migrating myoelectric complex (MMC).

Conversely, MU dosage forms (less than 2 mm in diameter) are thought to disperse in the stomach and empty from the fed stomach with the digestible contents. Investigations to evaluate the GE of MU dosage forms have, to date, not measured GI motility and transit simultaneously (Davis et al., 1984; O'Reilly et al., 1987; Wilding et al., 1991). It has therefore not been possible to determine whether MU dosage forms empty from the stomach with food or whether emptying occurs during the interdigestive phase. In the main, explanations for changes in GI transit have been extrapolated from the literature on GI motility.

The objective of the present study was to investigate the mechanism of GE of MU dosage forms in healthy male subjects, using the combined techniques of radiotelemetry and gamma scintigraphy to simultaneously measure GI motility and GI transit respectively.

Materials and Methods

Pellet manufacture

The cationic ion exchange resin, Amberlite IR-120 (BDH, Poole, Dorset), was regenerated and then sieved to provide particles in the size range 0.8–1.1 mm diameter. The resin was radiolabelled by soaking in a solution of ^{111}In chloride. The resulting slurry was dried in a fan oven at 60°C for 2 h. The beads were then placed into a size 2 hard gelatin capsule to a fill weight of 330 mg and their total activity checked such that each capsule contained 1 MBq of activity at the time of administration. The stability of the labelling procedure had been verified previously (Copping, 1985).

Radiolabelled meal

Radiolabelled eggs on toast were prepared using the standard method described previously by Knight and Malmud (1981). The scrambled eggs were labelled by the addition of ^{99m}Tc sulphur colloid to the ingredients before cooking to give an activity of 3 MBq at the time of administration. Coadministration of a radiolabelled meal with the radiolabelled pellets provided scintigraphic evidence of the dietary state (fed or fasted) of the subject.

Radiotelemetry

GI motility was measured using a pressure-sensitive RTC (Remote Control Systems, London). The RTC measured 25 × 8 mm with a battery life of 90 h. The RTC was radiolabelled with 1 MBq ^{99m}Tc, as a sealed source placed in the battery compartment. The RTC was enclosed within a rubber sheath to protect the pressure-sensitive diaphragm from faecal material and to facilitate cleaning after the study. The RTC was allowed to stabilize at 37°C for 12 h and was then calibrated before ingestion (Reynolds et al., 1989). Each RTC was individually tuned to its optimum receiving frequency (100–300 kHz) to prevent interference from other external electrical sources. The radio signal was detected by an aerial worn around the subject's waist.

Study protocol

The study was performed on eight, healthy, male subjects (age, 20–27 years; height, 162–180 cm; weight, 64–80 kg) who were non-smokers and were not on any medication. Each provided written informed consent prior to the start of the study and all subjects were judged to be in good physical health on the basis of medical history and the results of appropriate haematological and biochemical screens. The experimental protocol was approved by the Ethics Committee of the University of Nottingham and the study was 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.

The study was performed on four study days, with two subjects studied per day. The subjects remained fasted overnight and at 8.00 a.m. each received the radiolabelled test meal (one scrambled egg, one piece of lightly buttered toast and a cup of tea: 1200 kJ), which was consumed over a 5 min period. Anatomical markers were positioned both anteriorly and posteriorly over the right lobe of the liver to provide external reference points. The RTC and the capsule, containing the ^{111}In labelled pellets, were taken immediately after the meal along with 100 ml of water. Anterior and posterior images, each of 60 s duration were taken at regular intervals immediately after dosing using a gamma camera (General Electric Maxicamera) having a 40 cm field of view and fitted with a medium-energy parallel hole collimator. Images were acquired at approx. 5 min intervals for the first 2 h and then at 15 min intervals for the remainder of the day. The images were recorded using a Bartec computer system and stored on magnetic tape for subsequent analysis.

The subjects were not allowed further fluids or lunch until all the radiolabelled contents had left the stomach. Lunch consisted of two rolls, one packet of crisps and an apple (3800 kJ). An evening meal was provided at 6 p.m. which consisted of one regular pizza (4000 kJ) and imaging ceased at 12 h post-dose.

Motility measurements were recorded continuously onto a chart recorder throughout the study period. Each trace was analysed manually by an investigator who was without prior knowledge of the scintigraphic data. The RTCs were subsequently passed per rectum and were recovered by the subjects.

Data analysis

Administration of the radiolabelled meal allowed delineation of the stomach anatomy. The recorded scintigraphic images were analysed by drawing regions of interest around the stomach, and the activity in these regions quantified for both the radiolabelled meal and the pellets as described previously (O'Reilly et al., 1987). The countrate from the regions of interest were corrected for background radiation, radioactive decay and the overlap of the ^{111}In activity into the ^{99m}Tc channel. The activity in the stomach was calculated as the geometric mean of the counts from the anterior and posterior images, as described previously (Tothill et al., 1978), and GE profiles for both the radiolabelled meal and the pellets were established.

TABLE 1

Gastric emptying times of the radiotelemetry capsule (min)

Subject no.	Scintigraphy	Telemetry
1	195	189
2	315	317
3	230	222
4	103	110
5	168	170
6	204	204
7	176	168
8	409	419
Mean	225	225
SD	96	98
Median	200	197
Range	103–409	110–419

Results

The capsule entered the stomach rapidly and no adherence to the oesophagus was observed. The radiolabelled pellets were released rapidly from the gelatin capsule and were observed to distribute themselves to varying degrees within the stomach contents. The pellets which had mixed with the stomach contents then accumu-

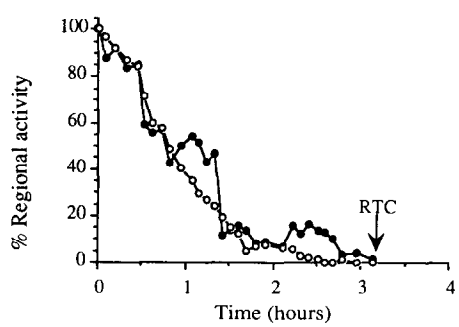

Fig. 1. Gastric emptying profiles of pellets (solid circles) vs food (open circles) for subject 1.

TABLE 2

Gastric emptying times ($T_{50\%}$) for the radiolabelled meal and pellets to empty the stomach (min)

Subject no.	Meal	Pellets
1	48	66
2	108	180
3	54	162
4	36	96
5	48	120
6	42	138
7	54	114
8	120	330
Mean	64	151
SD	32	81
Median	51	129
Range	36–120	66–330

lated in the distal stomach. This pattern of dispersion and accumulation was observed in all eight subjects. The RTC was located with the pellets in the distal stomach.

Examination of the motility traces allowed the GE time of the RTC to be determined. GE of the RTC was also established by scintigraphy and the data were in good accord with those determined by the telemetric technique (Table 1). The GE times for the radiolabelled food and the pellet formulation are provided in Table 2 and are represented as the time for half the activity to empty from the stomach ($T_{50\%}$). The GE time for the food is significantly faster than that reported for the pellet formulation ($p > 0.05$ Wilcoxon).

Figs 1–8 represent graphically the GE profiles for both the radiolabelled meal and the pellets.

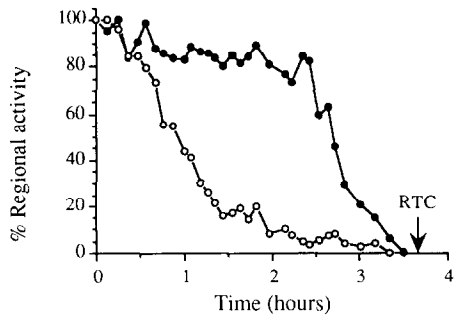

Fig. 3. Gastric emptying profiles of pellets (solid circles) vs food (open circles) for subject 3.

The GE times for the RTC, as assessed by telemetry, are superimposed onto the GE profiles. Visual inspection of the profiles reveals that there was a marked difference in the GE of the pellets and the meal for many of the subjects.

Discussion

Few studies have measured the GE of radiolabelled food and pellets simultaneously. Most have investigated pellet emptying, with conclusions being drawn by comparison and extrapolation of data from similar but separate studies investigating the GE of food. However, large inter- and intra-subject variations in GE have been reported (Coupe et al., 1991b). Therefore, in order to provide comprehensive results, it is preferable to administer preparations, in this case food and pellets, concurrently, each being labelled with a different radionuclide. In this way the relative

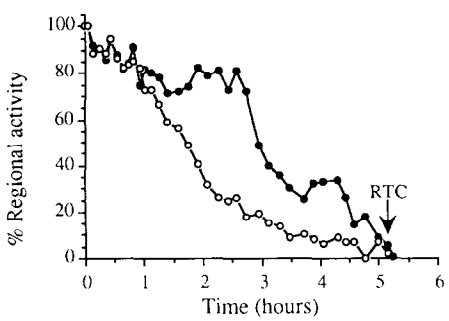

Fig. 2. Gastric emptying profiles of pellets (solid circles) vs food (open circles) for subject 2.

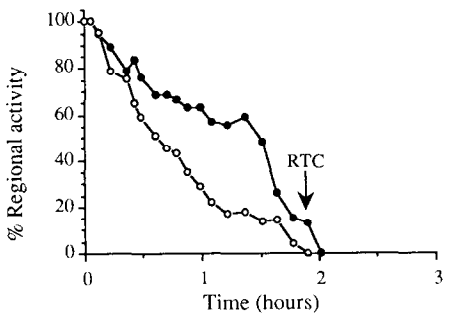

Fig. 4. Gastric emptying profiles of pellets (solid circles) vs food (open circles) for subject 4.

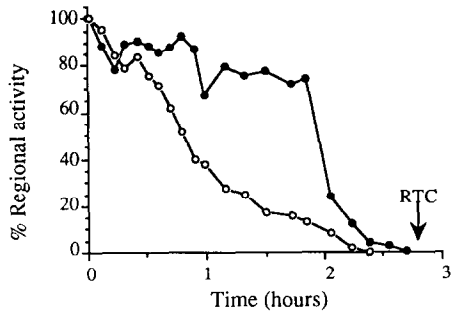

Fig. 5. Gastric emptying profiles of pellets (solid circles) vs food (open circles) for subject 5.

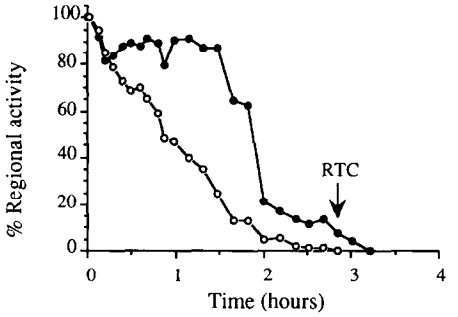

Fig. 7. Gastric emptying profiles of pellets (solid circles) vs food (open circles) for subject 7.

behaviour of the systems can be evaluated within the same subjects and the data are not affected by day-to-day variations that may have confused previous studies. From the GE profiles (Figs 1–8) it is evident that pellets do not empty concurrently with food. It is also evident that there is not one discreet mechanism which can adequately describe the GE of the pellet formulation.

The GE profiles for the radiolabelled eggs were similar for each of the subjects. A linear emptying slope followed by a slow final phase as the stomach becomes nearly empty was exhibited, which is characteristic of the emptying of solid food (Heading et al., 1976; Harris et al., 1987). A mean GE ($T_{50\%}$) of 64 ± 32 min was recorded which is in good agreement with previous data on the GE of radiolabelled scrambled eggs (Urbain et al., 1990).

In previous publications, GE has been expressed as a single mean profile (Christensen et al., 1985; Davis et al., 1987; Fischer et al., 1987; Ollerenshaw et al., 1987; O'Reilly et al., 1987). However, this approach could well mask highly important individual emptying patterns. The composite GE curve may not be an adequate approximation of any of the individual profiles. Indeed in this study, the GE of the pellets from the fed stomach did not follow just one trend.

Subject 1 exhibited an emptying profile which would be predicted from a review of current literature. Capsule disruption occurred rapidly and the pellets were then observed to distribute themselves widely throughout the stomach before emptying with the solid phase of the meal. GE ($T_{50\%}$) of the meal for this subject was 48 min, which agrees well with literature values for the GE of light meals (Christian et al., 1980). The GE ($T_{50\%}$) time for the pellets was similar (66 min). More importantly, the GE profiles of the food and the pellets were nearly superimposable (Fig. 1). The time for the food to empty completely from the stomach was approx. 2.5 h and this correlated well with the digestive motility pat-

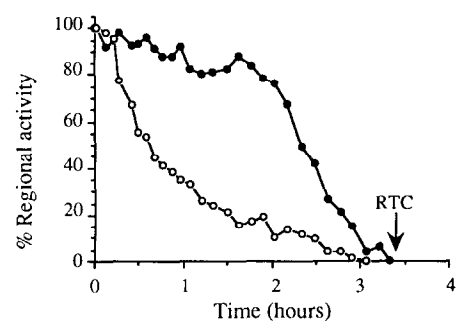

Fig. 6. Gastric emptying profiles of pellets (solid circles) vs food (open circles) for subject 6.

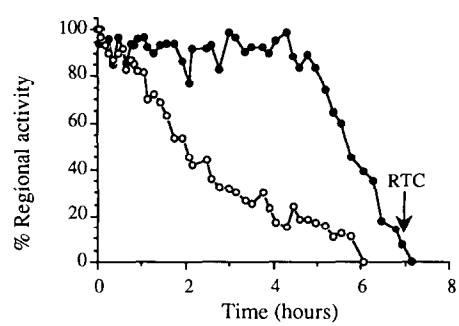

Fig. 8. Gastric emptying profiles of pellets (solid circles) vs food (open circles) for subject 8.

terns which lasted for about 2 h. The characteristic period of quiescence, associated with phase 1 of the MMC, followed the digestive activity and this lasted approx. 1 h. The RTC emptied from the stomach at 189 min post-dose with contractions associated with phase 3 of the MMC.

A similar pattern of emptying was observed for subject 4 (Fig. 4). The GE profiles were similar for both radionuclides suggesting a degree of mixing of the pellets with the food prior to GE. Interestingly, the RTC was observed to empty from the stomach at 103 min post-dose, prior to onset of the interdigestive activity. It is thought that the RTC emptied with the strong peristaltic contractions associated with the end of the digestive phase. As the stomach becomes progressively more and more empty, the peristaltic contractions begin further up the body of the stomach (Guyton, 1986). The peristaltic mixing contractions increase in strength and become very intense in the final stages of emptying, the pressure generated being much greater than that during the early stages of digestion, possibly leading to the emptying of the RTC.

The remaining six subjects exhibited a similar emptying profile. Capsule disruption was rapid and the pellets were seen to spread throughout the stomach. The pellets were then observed to regroup and position themselves in the body of the stomach. The differing intragastric distributions of the pellets and the concurrently ingested meal were consistent with those reported previously (Jian et al., 1982; Meyer et al., 1986, 1988). These studies demonstrated that markers of the different meal phases were not homogeneously dispersed in the gastric contents.

Other workers have observed similar separation of gastric contents following the administration of formulations of different densities. Davis et al. (1986) have observed scintigraphically the separation of formulations due to their density. Heavy and light pellets were mixed with a liquid meal and administered after a light breakfast. The scintigraphic images clearly showed that the light pellets floated on the stomach contents, whereas the heavy pellets were seen to reside at the lowest point of greater curvature of the stomach. The results indicated that the stomach can discriminate between materials of different densities. The effect of density on GE has been extensively investigated and conflicting results have been reported. Studies in dogs have shown that spheres with densities greater or less than 1 empty more slowly than spheres of the same size with a density of 1 (Meyer et al., 1985). Devereux et al. (1990) showed that the GE of heavy pellets was extended in both the fed and fasted state. Similarly, it has been shown that an increase in density from 1 to 1.6 g/cm^3 significantly delayed average transit times in ileostomy subjects (Bechgaard and Ladefoged, 1978). However, these latter findings were not confirmed in normal subjects. Studies by other groups (Davis et al., 1986; Kaniwa et al., 1988) have failed to show any significant differences due to density. The pellets used in the present study had a density of 1.2 g/cm^3, which was considered to be representative of many conventional pellet systems. Previous studies using similar pellets have not reported emptying differences to density attributable effects (Davis et al., 1984; O'Reilly et al., 1987; Wilding et al., 1991). However, none of the previous studies coadministered the pellets with radiolabelled food. If a mean GE profile, for both pellets and the radiolabelled meal, is calculated from the results of the present study (Fig. 9), it is very similar to other published mean results (Davis et al., 1987; Fischer et al., 1987; O'Reilly et al., 1987; Wilding et al., 1991). Thus, it is likely that the precise mechanism of GE for pellet formulations may have been oversimplified in the past.

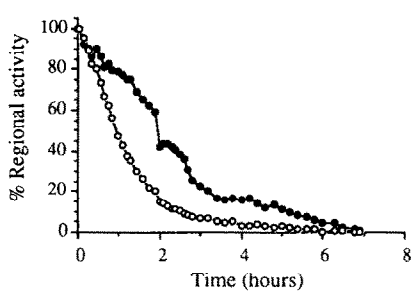

Fig. 9. Mean gastric emptying profiles of the radiolabelled food (open circles) vs pellets (solid circles).

Following a distinct lag phase, the pellets emptied rapidly in an almost bolus fashion in the remaining six subjects. Simultaneous monitoring of intraluminal pressure, via the RTC, provided an insight into the proposed emptying mechanisms. Emptying of the pellets occurred either towards the end of the digestive phase (subjects 2, 3 and 5–7) or during phase 2 and 3 (subject 8) of the MMC. Gastric activity increases as the stomach becomes progressively more empty and therefore it is suggested that the pellets reside in the base of the stomach away from the antral flow. Emptying then only occurs when the stomach becomes nearly empty and the contractions increase in both force and originate further up the stomach. Pellets can, however, resist these contractions (subject 8) and are then emptied later with the phase 2 and 3 contractions of the MMC. Similar findings have been reported in both dogs (Heinamaki et al., 1988) and humans (Marvola et al., 1989) following the administration of barium sulphate pellets (density 1.35 g/cm^3).

The effect of particle size on GE may also be contributing to the mechanism of pellet emptying. The ability of the stomach to discriminate between solid and liquid emptying has been reported previously (Heading et al., 1976; Carryer et al., 1982). It is conceivable that the stomach can discriminate between particles less than 2 mm in size and food. Although the GE of large particulates in relation to food has been extensively studied, few studies have looked at the GE of small particles. The GE of concomitantly administered radiolabelled liver and 1.6 mm spheres was investigated in healthy humans (Meyer et al., 1988). In three of the 16 subjects, the 1.6 mm spheres failed to empty the stomach within 210 min, whilst in a further two subjects the spheres exhibited a lag time in excess of 2 h before empting commenced. No mechanism to describe the results was suggested, however, it was noted that the effect was observed more frequently with increasing diameter of spheres. The results are in accord with those presented in this study and suggest that the stomach can discriminate between particles of less than 2 mm in diameter and digestible food.

The emptying properties of particles between 1 and 3 mm in diameter and their relationship to the GE of food has also produced conflicting results. Plastic spheres (3 mm in diameter) have been found to empty nearly as fast as (Bertrand et al., 1980) or considerably slower than (Jian et al., 1983) concurrently ingested food. Similarly, 3 mm paper squares were found to empty slower than (Holt et al., 1982) or faster than chicken liver (Guller et al., 1977). Meyer et al. (1988) undertook a study to investigate the size of spheres which could empty the stomach at the same rate as concomitantly administered food. They evaluated the concurrent GE of spheres (1–3 mm in diameter) labelled with ^{113m}In and chicken liver labelled with ^{99m}Tc. Spheres (1 mm in diameter) emptied consistently faster than 2.4 or 3.2 mm spheres and statistical analyses indicated that spheres 1.4 ± 0.3 mm in diameter emptied at the same rate as ^{99m}Tc labelled liver.

A further factor that could influence the GE results is the fact that the stomach is anatomically arranged to hinder particle movement. The stomach's position is fixed at the upper end to the diaphragmatic hiatus and at the distal pyloric end. Between these two points it relaxes in response to volume distension and as it relaxes the most dependent portion of the stomach, the antrum, extends downward below the pyloric outflow tract. It has been postulated that the downward dilatation of the gastric antrum forms a type of U-shaped trap for solid particles which hinders movement through the pylorus (Meyer, 1989).

The failure of some groups to report different emptying trends may be as a consequence of the tendency to summarize the data as a mean curve. In a few publications the effect of plotting a mean curve, when the individual data are different, is demonstrated quite clearly, since the authors have supplied both sets of information (Bechgaard et al., 1985; Davis et al., 1986). In each case the individual curves describe several different patterns of emptying, with delayed emptying occurring in at least one subject. Once the mean curve was plotted however, such features were no longer apparent.

From these and the other reported findings it is clear that the stomach represents a complex

system which differentiates between differences in density, size and meal composition. It therefore appears likely that the emptying process of pharmaceutical dosage forms cannot be described by one mechanism and indeed many processes are probably involved which vary both within and between subjects.

Conclusions

The combined techniques of radiotelemetry and gamma scintigraphy have allowed the mechanisms of GE of a pellet dosage form and a coadministered radiolabelled meal to be investigated. Emptying of the pellet formulation from the stomach did not follow a trend and in only two of the eight subjects did the pellets empty from the stomach concurrently with food. In the remaining six subjects, the radiolabelled meal emptied from the stomach in advance of the pellets, which showed delayed GE. In one subject, the pellet formulations resisted emptying during the post-prandial phase and emptied from the stomach with the contractions associated with phase 2 and phase 3 of the interdigestive MMC.

It is evident from the literature that the mechanism by which small particles empty from the stomach has still to be fully elucidated and it would appear that the stomach can differentiate between small particles and concurrently administered food.

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