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The gastric emptying of food as measured by gamma-scintigraphy and electrical impedance tomography (EIT) and its influence on the gastric emptying of tablets of different dimensions

Fridrun Podczeck, Catherine L. Mitchell, J. Michael Newton, David Evans and Michael B. Short

Abstract

A study in human volunteers has been designed to evaluate the influence of different food regimes on the gastric emptying of 3 mm and 10 mm diameter tablets. Dextrose and beef drinks were used as liquid food; a mixture of minced beef and mashed potato (shepherd's pie) was used as a solid meal. The gastric emptying of these foods was monitored simultaneously with electrical impedance tomography (EIT) and gamma-scintigraphy (GS), and was quantified in terms of the time before gastric emptying started, the lag time, the mean gastric residence time (MGRT) and its variance (VGRT), and the time for complete emptying. The gastric emptying time of the tablets was established by monitoring the position of the tablets, which had been labelled with suitable radio isotopes, by GS. The two systems for monitoring gastric emptying of the foods did not provide equivalent results: times obtained with EIT were generally shorter than those obtained with GS for the liquid foods, but were longer for the solid meal. There was only a slight difference in the emptying times of the two liquid foods, whereas values for MGRT, VGRT and the time for complete emptying were considerably longer for the solid meal. In nearly all instances the tablets emptied after the foods had emptied completely from the stomach. Gastric emptying times were longer for the 3 mm tablets than the 10 mm tablets, whatever food they were taken with. The difference between the median emptying times was significant when the meal was either a dextrose solution or a beef drink, but not when the meal was shepherd's pie. The increase in gastric emptying time of tablets induced by solid food was greater than that associated with the differences in tablet size. By providing a protocol that did not allow the administration of further food until after the tablets had emptied from the stomach, no tablet emptying times exceeded 6 h.

School of Health, Natural & Social Sciences, University of Sunderland, City Centre Campus, Wharncliffe Road, Sunderland SR1 3SD, UK

Fridrun Podczeck

School of Pharmacy, University of London, Brunswick Square, London WC1N 1AX, UK

Catherine L. Mitchell, J. Michael Newton

The Wingate Institute, St Bartholomew's and Royal School of Medicine, 26 Ashfield Street, London E1 2AJ, UK

David Evans

Medical Physics, University College London, Keppel Street, London WC1E 6AD, UK

Michael B. Short

Correspondence: Professor Michael Newton, The School of Pharmacy, University of London, 29/39 Brunswick Square, London WC1N 1AX, UK. E-mail: michael.newton@pharmacy.ac.uk

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Introduction

Unit solid dosage forms, which empty from the stomach as a single unit, are usually used to protect drugs from gastric acid by enteric coating, or to provide controlled release of drug (coated tablets, matrix tablets, osmotic devices). There have been numerous studies of the process of gastric emptying, and Olsson & Holmgren (2001) pointed out that almost everything appears to affect the rate of gastric emptying. The emptying of a single unit from the stomach can be expected to depend on several factors, but food is one of the most important factors in terms of affecting dosage forms. In a recent review, Camilleri (2006) divided the response of the gastrointestinal (GI) tract to food intake into three integrated but overlapping phases: cephalic, gastric and intestinal. The initial cephalic phase is associated with the various gastric secretions and control of the motor response. Motor responses can be divided into 'fasting' and 'postprandial'. The former is characterised by the interdigestive migrating motor complex (sometimes called the migrating myoelectric complex, MMC), the phases of which have been described by Furness & Costa (1987) as: phase 1 – quiescent; phase 2 – irregular single contractions, and phase III – intense rhythmic contractions. Ingestion of a meal changes the motor activity, altering the tone of the muscles and allowing an increase in the proximal and distal stomach volumes without an increase in pressure

(Camilleri 2006). Where the food is in contact with the GI tract, the MMC is replaced by contractions of variable frequency and amplitude, which are associated with the mixing and digestion of the meal. The maximum contraction frequency is usually lower than during phase III of the MCC. Camilleri has also investigated the relationship between antral motility and gastric emptying of solids and liquids (Camilleri et al 1985). Their data were consistent with antral pressure begin responsible for triturating solid food, and the role of the antrum in the subsequent propulsion of solids and liquids from the stomach. This provides the classic concept of material being stored in the fundus and then being delivered to the antrum from above, from where it is delivered to the duodenum, at a rate controlled by opening of the pyloric sphincter. However, using computer modelling and comparison with magnetic resonance imaging (MRI), Pal et al (2007) have recently proposed the existence of a 'Magenstrasse' or 'stomach road', which can direct liquid content from the far reaches of the fundus directly into the intestine within 10 min, rather than waiting to be brought up from the bottom of the antrum, which may have implications for drug delivery.

The description above relates to the gastric emptying of food, the solid component of which is digestible (i.e. can be physically reduced in size). However, when objects that are not digestible, such as tablets, are swallowed, the size of the object is a further factor that could influence its emptying. Evidence for the size threshold above which an object is treated by the stomach as a solid rather than a liquid is conflicting. A threshold value of 2 mm is often quoted, but this comes from studies in dogs (Kelly 1980); the same value of 2 mm in humans has been reported by MacGregor et al (1977) and Meyer et al (1981). Clarke et al (1993) clearly demonstrated that when pellets as small as 0.5 mm were administered to fasted human volunteers, the emptying process differed from that of a liquid. The pellets appeared to empty in 'quanta' over a prolonged period, rather than continuously like liquid. Hence, the pellets behaved as a solid. In terms of tablets, Khosla et al (1989) reported that the nature of the co-administered meal was more important than the difference in tablet size (between 3 and 7 mm) when multiple tablets were administered. A greater variability in the emptying rate was claimed for the larger tablets. In a later study, Khosla & Davis (1990) reported that 7 mm and 11 mm diameter tablets could empty from the fed stomach, but 13 mm tablets could not. However, both these studies lacked accuracy in the estimation of gastric emptying times, and used parametric statistical analysis to process data that were non-parametric in nature. Podczeck et al (1999) described an alternative approach to estimating the gastric emptying time of single objects, demonstrating the need for frequent measurements of the position of the tablet within the GI tract. This approach was used to describe the emptying of 6.6 mm diameter tablets (Podczeck et al 2007a) and these results were compared with their previous findings for 12 mm diameter tablets (Podczeck et al 1999). This approach has also been used to characterise the initial and final gastric emptying of several 3.2 mm diameter tablets (Podczeck et al 2007b) and the gastric emptying of capsules used to deliver drugs to the colon (Tuleu et al 2002). All these studies involved fasted volunteers.

Several studies have used gamma-scintigraphy to investigate the influence of food on the gastric emptying of tablets. In these studies the transit of a tablet labelled with a radioactive marker is monitored by a gamma camera. Food clearly has an effect on tablet transit, but the reported magnitude of the effects is questionable in several instances for various reasons.

The problems that arise here vary. One problem is identifying the actual position of the tablet within the GI tract, as the image only provides information on the position of the radioactivity, without any information on the GI tract itself. This can be subjective and even if a liquid marker is used to outline the GI tract, this will move at a different rate to the solid and will be subjected to dilution by secretions within the GI tract. In some cases, this identification is not helped by the use of only a single image (e.g. Hardy et al 1987, Mojaverian et al 1989, Sugito et al 1990, Kenyon et al 1994), usually an anterior view, as opposed to an anterior and posterior image and derivation of a geometric mean (e.g. Clarke et al 1993, Podczeck et al 1999, Podczeck et al 2007a, b). A method that allows depth correction of single images has been used with anterior images of emptying of solid foods (Meyer et al 1983), but was not applied in the above studies with anterior images.

Many studies give no details of the frequency of image collection (e.g. Davis et al 1986; Hardy et al 1988; Khosla et al 1989; Khosla & Davis 1990; Coupe et al 1991; Abrahamsson et al 1996). When time intervals are specified, the shortest is 10 min (Kenyon et al 1994), while 20 min (Hardy et al 1987) or 30–45 min intervals have also been reported (Mojaverian et al 1989; Sugito et al 1990). Sangekar et al (1987) described a regime whereby volunteers were monitored continuously for 30 min, followed by a gap of 30 min. As we have demonstrated previously, short time intervals – of the order of 3 min – are required to obtain a reliable measure of the gastric emptying time of a single object (Podczeck et al 1999). As food extends the time at which a tablet empties from the stomach, there is a tendency to use longer time intervals when evaluating the position of the tablet, usually to 30 min, which will result in considerable error in estimating the emptying time.

A further factor that has complicated identification of the effect of tablet size is the administration of more than one tablet (Davis et al 1988; Hardy et al 1988; Khosla et al 1989; Khosla & Davis 1990; Sugito et al 1990; Coupe et al 1991). Hence, gastric emptying times are expressed as mean values for two tablets or, for multiple tablets, as the time for 50% of tablets to empty.

The calorific value of the meal is known to influence gastric emptying (Hunt & Pathiak 1960; Hunt 1983). It is therefore surprising that the calorific value of food administered with the tablets is frequently not reported (e.g. Hardy et al 1987, 1988; Sugito et al 1990; Coupe et al 1991). Another factor that influences gastric emptying when tablets are administered after food is the timing of the next meal. As observed by Ewe et al (1991), if a meal is given while the tablet is still in the stomach, then gastric retention can be extended. This appears to have happened in several studies that involved a fixed protocol of providing a meal at a set time after administration of the dose, instead of waiting for the tablet to empty before allowing the second meal to be consumed. This could explain the extended gastric emptying times reported by

Cortot & Colombel (1984), Hardy et al (1987), Mojaverian et al (1989), Sugito et al (1990), Kenyon et al (1994) and Abrahamsson et al (1996).

While the importance of the MMC is often mentioned, only one study (Coupe et al 1991) made any attempt to measure the state of the digestive tract in the volunteers studied. They used a pressure-sensitive remote control system to assess the status of the MMC cycle in the volunteers. These latter workers, along with Mojaverian et al (1989), are among the few who have actually monitored the emptying of the food by labelling with a radioactive marker, so that information on the emptying of the food in relation to that of the tablet could be provided.

As we have previously pointed out (Podczeck et al 1999), a further problem with many of the papers cited above is that they all treat the data for the gastric emptying time as being an actual value instead of an estimate of the true event. This leads to comparisons of the values using parametric statistics, which should not be used for such estimates. In view of these issues, it is not possible to provide a definitive answer to the question of the influence of tablet size on their emptying from the stomach when given in the fed state.

We report here a study of the influence of food on gastric emptying, comparing 3 mm and 10 mm diameter tablets administered simultaneously with radiolabelled solid and liquid meals of differing calorific value. The gastric emptying of both food and the tablets was monitored by gamma-scintigraphy. In addition we used electrical impedance tomography (EIT), a non-invasive technique, to follow the emptying of the food. This technique does not require radiolabelling of the food. Gamma-scintigraphy is considered to be the 'gold standard' for determination of gastric emptying (Hellstrom et al 2006); however, EIT could provide a cheaper system and reduces the amount of radioactive material administered to volunteers.

Materials and Methods

Materials

Tablets were prepared from lactose USNF23 (Sheffield Products, Norwich, NY, USA), polyvinyl pyrrolidone (PVP) and magnesium stearate, both Eur Pharm (BDH Ltd, Poole, Dorset UK). For the 3 mm diameter tablets, the ion-exchange resin Dowex 50W-8H (BDH Ltd, Poole, Dorset, UK) was incorporated into the granulation; for the 10 mm diameter tablets, Amberlite CG400 9 (Aldrich Chemicals Co Ltd, Gillingham, Kent, UK) was used.

Preparation of tablets

The study was undertaken before the European Union requirement that all human trials should be conducted under Good Manufacturing Practice (GMP) conditions. All procedures involved in the preparation of tablets were undertaken under 'clean' conditions under the supervision of one of the authors (John Michael Newton) who is a Qualified Person under the Medicines Act.

The formulae of the tablets are given in Table 1. Tablets were compressed from granules prepared by wet granulation.

Table 1 Percentage composition of tablets

	3 mm tablet	10 mm tablet
Lactose	89	89
Polyvinyl pyrrolidone	5	5
Amberlite CG400	5	0
Dowex 50W-8H	0	5
Magnesium stearate	1	1

Lactose, PVP, ion-exchange resins and water were mixed in a planetary mixer (Kenwood Chef, Kenwood Ltd, Havent, Hants, UK). The wet mass was pressed through a 1.7 mm mesh sieve and dried at 60°C for 3 h. Once dry, the granules were sieved through a 1.00 mm sieve and any fines were removed with a 0.25 mm mesh sieve. The dry granules were blended with 1% magnesium stearate by rotating in a screw-cap jar on rollers for 5 min. The 10 mm diameter tablets were compressed with normal concave punches on a rotary tablet machine (Model D, Manesty Machines, Speke, UK) operated by hand. The 3 mm tablets required the removal of granules greater than 0.71 mm and the addition of 1% Aerosil 200 (Degussa, Frankfurt, Germany) and special compaction conditions and were specially made for the study by Nordmark GmbH (Lübeck, Germany). These tablets were compressed under GMP conditions.

Tablet coating

The tablets were coated in a fluid bed coater (Aeromatic Strea-1 ACM Machinery, Tadley, UK). The coating solution consisted of 5% ethyl cellulose N50 grade (Hercules, Delaware, USA), 1.2% diethylphthalate (McCarthy's, Romford, UK), 2.4% PEG 4000 (Koch-Light Ltd, Berkshire, UK) in a 70:30 mixture of dichloromethane and methanol (both BDH Ltd, Poole, UK). The coating solution was sprayed through a 0.8 mm nozzle at a rate of 0.8 mL min^{-1} with an inlet air temperature of 50°C. Sufficient coating solution was applied to ensure that the tablets did not disintegrate after 3 h in simulated gastric fluid followed by 21 h in simulated intestinal fluid, when tested in a standard disintegration tester. The final tablet diameters were 3.2 mm and 10.2 mm.

Radiolabelling of tablets

The 10 mm tablets were soaked in 10 mL sodium pertechnetate solution that had been obtained from a generator (Elumatic III, Cis, France) for 5 h with automatic agitation. The 3 mm tablets were soaked for the same time in a solution of ^{111}In chloride (Amersham International, Amersham, UK). The tablets were removed from the radioactive solutions and washed twice with 5 mL normal saline, followed by soaking for 1 h in normal saline. The tablets were removed from the saline, excess liquid removed, and the tablets dried overnight at 40°C. On the morning of use, the radioactivity of the tablets was measured with an isotope calibrator (Model 270, Pitman Instruments, Surrey, UK): the 10 mm diameter tablets contained approximately 7.4 MBq and the 3 mm tablets 3.5 MBq.

Test meals

A low-nutrient fluid was prepared by dissolving dextrose (Eur Pharm; BDH Ltd, Poole, UK) in drinking water to produce a 5% solution. For a nutrient liquid, a beef drink (Oxo, Brooke Bond Foods, Banbury, UK) was prepared by dissolving two beef extract cubes in boiling drinking water and cooling to 45°C for administration. Shepherd's pie – a mixture of beef mince and instant dried potato mixture (Sainsburys plc, London, UK) was chosen as a solid meal. The radioactive solution was added to 150 mL boiling water and mixed with 40 g dried potato, to give 200 mL mashed potato, which was placed on top of 200 mL minced beef and onion, then heated to 45°C. Each of the meals was radiolabelled with ^{113m}In diethylenetriamine pentaacetic acid, obtained from a Sn/Tc generator (Amersham International, Amersham, UK), by adding the appropriate quantity to the drinks or solid meal to provide a level of activity equivalent to approximately 7.0 MBq of activity at the time of administration. The characteristics of the meals and their conductivity are given in Table 2.

Study protocol

The study was undertaken before the requirement for dosage forms to be prepared under GMP conditions. The study was approved by the University College and Middlesex School of Medicine Ethics Committee, with a certificate of approval from the Administration of Radioactive Substances Advisory Committee. It was carried out in accordance with the provisions of the Declaration of Helsinki (1965) with the revision of Tokyo (1975) and Venice (1983). Each volunteer received a full explanation of the nature and purpose of the study and provided written consent.

Ten healthy men (aged 18–58 years) participated in an open comparative study. Each volunteer was assigned three study days, separated by at least 3 days. Test meals were given in a random order. Volunteers ate a standard evening meal (spaghetti bolognese, Tesco Stores Ltd, Cheshunt, Herts, UK) at a time to ensure a 12-hour fast before the test procedure. They were asked to abstain from spicy foods and alcohol for 24 h before the test. After consuming the given meal on the day of the test, no further food was allowed for 6 h or until the meal and the tablet had left the stomach, which ever was longer.

Electrical impedance tomography (EIT)

EIT is a non-invasive approach to measuring gastric emptying and is based on the principle of generating tomographic images of local tissue resistivity (Avill et al 1987). As a meal of higher or lower conductivity than the surrounding tissue enters or leaves the stomach, the distribution of resistivity in the upper abdomen changes. Sequential images of the tissue resistivity can be used to derive profiles of gastric filling and emptying. The conductivity values of the meals are provided in Table 2.

An APT Mark I (IBEES, Lodge Moor Hospital, Sheffield, UK) was used for the EIT measurements. The system consists of a data collection unit, personal computer, visual display monitor and printer. Sixteen pre-gelled silver/silver electrocardiography electrodes (Medicotest Ltd, Bristol, UK) were placed in a ring around the upper abdomen at the level of the costal margin and connected to the data collection unit. A current of 1 mA at 50 kHz passes between two adjacent electrodes termed the 'drive electrodes'. The potential difference is measured at the remaining pairs of electrodes. Each pair of electrodes in turn becomes the drive electrodes as the cycle is repeated. A total of 208 measurements are made during each cycle. A reference data set is established initially; subsequent data sets are back projected against the reference data set to produce an image of the change in tissue resistivity in the electrode plane. Tomographic images are visualised on the display monitor. Baseline resistivity was established for 10 min before the test meal was consumed to set up a region of interest. The change in impedance within the region of interest was calculated for the study images and expressed as a percentage of the change in impedance from the baseline. Images were acquired every minute for up to 6 h or until the meal had left the stomach.

Gamma-scintigraphy

A Siemens 'Rota' camera (Siemens UK, Bracknell, UK) system with two opposed ZLC detectors, each with a 40 cm field of view, was used, with the volunteer seated between the two detector heads. Each detector was fitted with a low-energy parallel-hole collimator suitable for the ^{99m}Tc, ^{111m}In and ^{113m}In imaging. Simultaneous anterior and posterior information was acquired, for 60 s for each isotope, providing an image for each system every 3 min, the frequency needed to identify differences in tablet emptying behaviour suggested from our previous studies (Podczeck et al 1999). The camera was connected to an on-line ADAC digital computer (DPS 3300, San Jose, CA, USA), allowing storage of data on the hard disk for processing and on magnetic tape for archiving. The position of the volunteer was marked with a ^{99m}Tc anatomical marker on the right subcostal margin. Imaging was continued for 6 h or until the meal and the tablets had left the stomach, which ever was longer. The counts recorded for the stomach area of interest from each detector were counted by

Table 2 Constituents and properties of meals

Test meal	Volume (mL)	Energy (kJ)	Protein (g)	Carbohydrate (g)	Fat (g)	Fibre (g)	Sodium (g)	Conductivity (mS cm^{-1})
Dextrose 5%	300	247.5	0	15.0	0	0	0	0.51
Beef drink	400	166.0	2.8	3.6	0.8	0	n/a	16.38
Shepherd's pie	400	956.8	8.9	10.3	19.2	0.6	0.44	13.28

computer and corrected for acquisition time. From the net counts, the geometric mean count was calculated, corrected for decay and overlap from the count of the tablets and finally expressed as a percentage of the initial counts.

Evaluation of gastric emptying characteristics of the food

The two systems used to evaluate the emptying of meals from the stomach are similar in their output, in that the percentage remaining in the stomach as a function of time is obtained. EIT provides values every minute but does give significant fluctuations. The graphs obtained from gamma-scintigraphy represent a 3 min time interval, as counts for the two tablets were taken between recording the counts for the radioactivity label of the food. The parameters chosen to represent the process of gastric emptying were derived from the gastric emptying curve (i.e. the percentage material remaining in the stomach as a function of time $P_t = f(t)$), and are the lag time (i.e. the time at which there was the first loss of the solid meal from the stomach) and the mean gastric residence time (MGRT), which is an estimate of the central tendency of the process of emptying (Podczeck at al 1995). MGRT is obtained from the gastric emptying curve using the simple trapezoidal rule:

$$MGRT = \frac{\int_0^{t_{max}} t \cdot P_t \, dt}{AUC}$$

where AUC is the area under the gastric emptying curve.

The variance of the gastric emptying process (VGRT; (Podczeck et al 1995) is obtained form the same curve by the expression:

$$VGRT = \frac{\int_0^{t_{max}} t^2 \cdot P_t \, dt}{AUC} - MGRT^2$$

The values of MGRT and VGRT describe the gastric emptying data in the same manner as an arithmetic mean and standard deviation would describe a sample of ratio data.

Times for complete stomach emptying

It is important to remember that gamma-scintigraphy and EIT have an important difference in how they see the process. Gamma-scintigraphy measures the presence of the radioactive label, so it assumes that the radiolabel stays with what is being measured. In the case of the liquid meals this is not an issue. With the solid meal, however, there is always the chance that some loss from the solid can occur, and only the carbohydrate portion of the food is labelled. In-vitro tests of the present system seem to show good attachment of the radiolabel and it is unlikely that the potato and meat portions of the meal will move at very different rates.

EIT measures the total impedance of the system, which is related to the total gastric content. This could change because of the addition of saliva and gastric secretions into the stomach, which can be up to 4500 mL per day (Burd & Lentz 2001), corresponding to about 3 mL per min. This is thought to explain the difference in emptying times between gamma-scintigraphy and EIT over the longer emptying times, leading to the suggestion that acid secretion should be inhibited to ensure equivalent values (Mangnall et al 1991). This would require the administration of a suitable drug, which was not considered to be appropriate for the short emptying times of the liquid meals, and would change the normal conditions of use for the solid meal.

Gastric emptying of the tablets

The first time that the tablet appeared to be out of the stomach was recorded, which will have a maximum error of 2 min.

Data analysis

All statistical calculations for samples (i.e. arithmetic mean, s.d., median values and interquartile ranges), and statistical tests were performed using SPSS 15.0 (SPSS Inc., Woking, UK). The median and interquartile range for the gastric emptying profiles were determined using the Bernoulli random event probability distribution approach, as described previously (Podczeck et al 1999).

Wilcoxon signed-rank test was used to compare emptying times for the two tablet sizes with one meal at a time. The Friedman test was used to compare the effects of different meals on emptying of one tablet size at a time, because the data presented are dependent samples (Snedecor & Cochran, 1980).

Results and Discussion

Comparison of the two methods characterising gastric emptying of food

Figure 1 shows results for the gastric emptying process for the three different meals in one volunteer. In some cases technical problems made it impossible to obtain a complete picture of the emptying of the meals (once each for the dextrose drink and the shepherd's pie with gamma-scintigraphy, and once for the beef drink with EIT). It was always possible to obtain a gastric emptying time for the tablets. Estimation of the lag time and the time for complete emptying of the meals presented some problems with both systems, and there is a degree of subjectivity in the values quoted. A lag time before the 'food' starts to empty from the stomach is usually associated with solid meals and not liquids (Hellstrom et al 2006). Except for two subjects, the values for the lag time obtained with the EIT system are all considerably longer than those obtained with gamma-scintigraphy (Figure 2). The start of gastric emptying, as indicated by gamma-scintigraphy, is never longer than 40 min. Addition to the stomach volume by gastric secretion does not appear to offer a satisfactory reason for the extended time estimates with the EIT measurements. As appreciable quantities of radioactivity have to be emptied before emptying

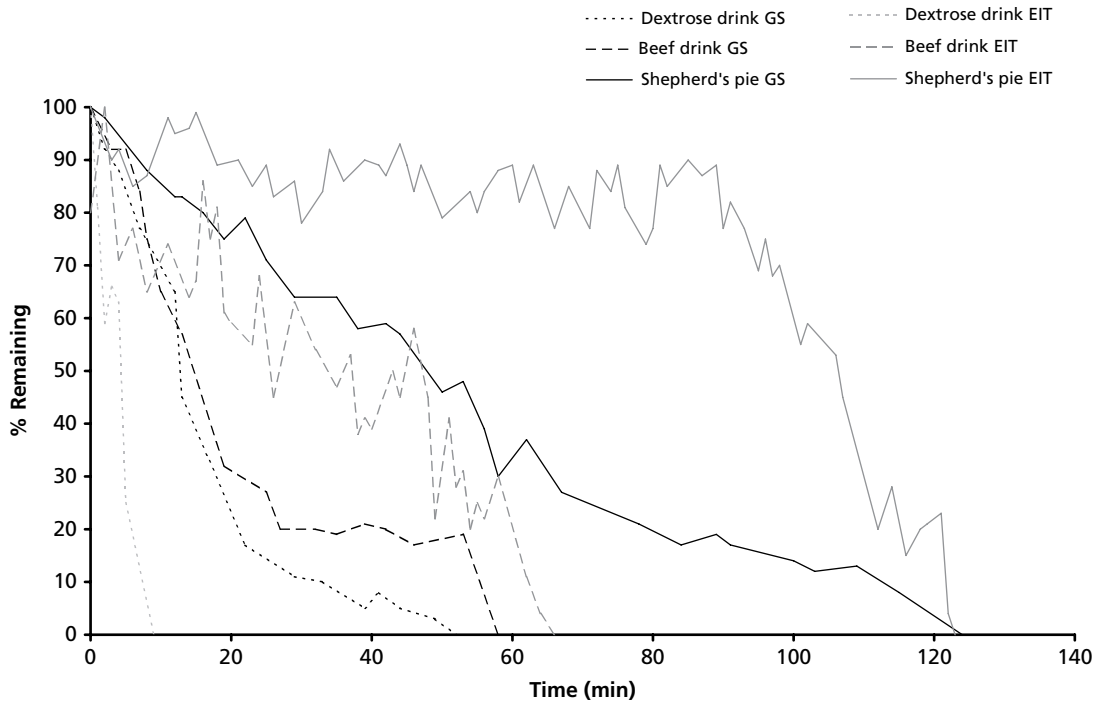

Figure 1 Gastric emptying profile of the three test meals for volunteer 7, measured by electrical impedance tomography (EIT) and gamma-scintigraphy.

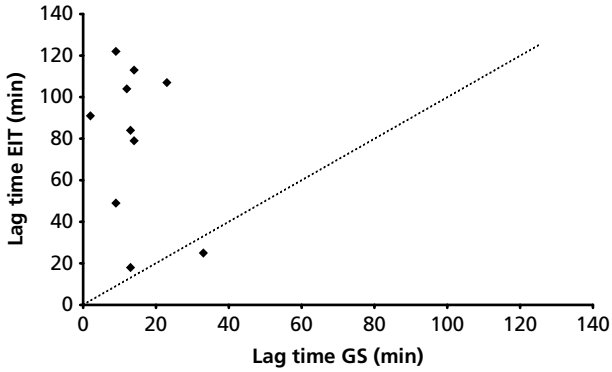

Figure 2 Comparison of gastric emptying lag time for the solid test meal (shepherd's pie) determined by electrical impedance tomography (EIT) and gamma-scintigraphy (GS). The dotted line symmetrically dividing the coordinate space indicates the position of data points if there were a perfect correlation between X and Y.

of the food can be detected, the gamma-scintigraphy measurements seem to indicate that there is some time before emptying of the solid component starts to occur. This might be because of the label leaching from the mashed potato to which it was added, because the potato might have emptied at a different rate to the minced meat. If the label were lost from the potato it would be expected to go into the liquid in the stomach, which could exit the stomach in spite of closure of the pyloric sphincter. However, EIT did not appear to detect any loss of liquid.

The values for MGRT with the two systems are compared in Figure 3. For the dextrose drink, the values given by EIT are always considerably less than those for the gamma-scintigraphy. There is a better agreement between the two systems in the case of the beef drink, except for one volunteer, where the value from gamma-scintigraphy is considerably

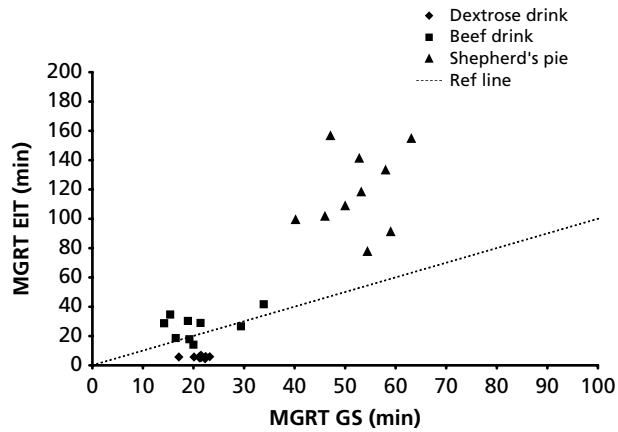

Figure 3 Comparison of mean gastric residence time (MGRT) for liquid test meals (dextrose drink and beef drink) and the solid test meal (shepherd's pie) determined by electrical impedance tomography (EIT) and gamma-scintigraphy (GS). The dotted line symmetrically dividing the coordinate space indicates the position of data points if there were a perfect correlation between X and Y.

larger than that for EIT. For the solid meal, values of MGRT obtained from EIT were always greater than those from gamma-scintigraphy, which may reflect the contribution of the secretions added to the stomach contents. As the values are often doubled, this contribution does appear quite high, suggesting that other factors may be involved.

Values for the VGRT show the same lack of correlation in the case of the dextrose drink (Figure 4), where the values obtained by EIT are considerably lower than those obtained by gamma-scintigraphy. There is a greater similarity for the beef drink, but even here there is not a good correlation. The VGRT values for the solid meal determined by EIT are considerably less than those determined by gamma-scintigraphy in 8 out of the 10 subjects, which is contrary to the results for the MGRT values. This suggests that gamma-scintigraphy appears to see the emptying process taking place over a longer period of time.

Complete emptying of food from the stomach can be difficult to identify. The effect of continuous addition of secretions to the stomach contents introduces variability into the EIT method. With gamma-scintigraphy it can be difficult to ensure that only the activity in the stomach region of interest is considered, in view of the changing dimensions and position of the stomach. For the dextrose drink, there is no agreement between values for complete stomach emptying from EIT and gamma-scintigraphy (Figure 5), EIT values consistently indicating a much shorter time period. The results for the beef drink are more variable, with EIT indicating both lower and higher values than gamma-scintigraphy, depending on the subject (Figure 5). For the solid meal, there is the tendency for the values obtained with EIT to be greater than those from gamma-scintigraphy (Figure 5). This could just reflect the response of added secretions to the meal, which could be significant over the longer time period of observation required for the solid meal to empty.

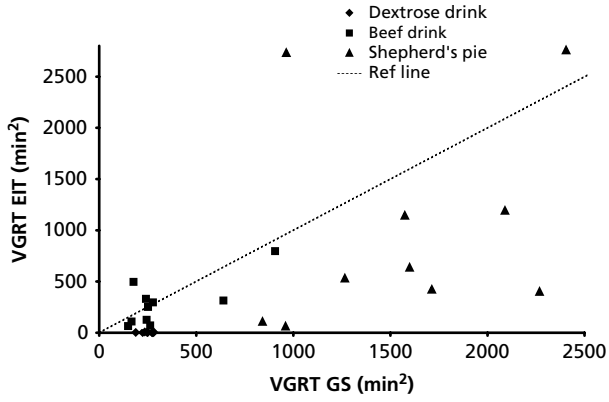

Figure 4 Comparison of the variance in gastric residence time (VGRT) for liquid test meals (dextrose drink and beef drink) and the solid test meal (shepherd's pie) determined by electrical impedance tomography (EIT) and gamma-scintigraphy (GS). The dotted line symmetrically dividing the coordinate space indicates the position of data points if there were a perfect correlation between X and Y.

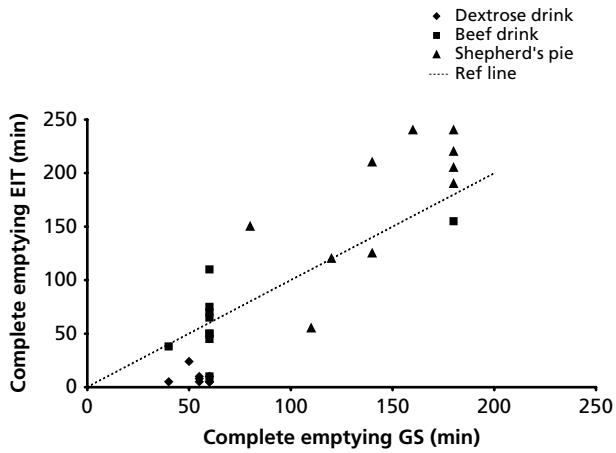

Figure 5 Comparison of the times for complete gastric emptying of liquid test meals (dextrose drink and beef drink) and the solid meal (shepherd's pie), determined by electrical impedance tomography (EIT) and gamma-scintigraphy (GS). The dotted line symmetrically dividing the coordinate space indicates the position of data points if there were a perfect correlation between X and Y.

Relation of tablet emptying to food emptying characteristics

As discussed in the Introduction, studies of the influence of tablet size on gastric emptying are largely unreliable, for various reasons; it is therefore inappropriate to make comparisons between these and the current results.

Emptying of the tablets would not be expected to occur in the lag time before the food emptied from the stomach, and this was not observed. Using MGRT values as characteristic of gastric emptying, the tablet emptying time is always after this value, whether this is measured by EIT or gamma-scintigraphy. The values of MGRT determined by EIT tended to be longer than when assessed by gamma-scintigraphy for the dextrose meal but were always shorter for the solid meal. When the tablet emptying time is compared with the time for complete emptying of the food, tablets always empty before complete emptying of the dextrose drink according to EIT (Figure 6a). However, with gamma-scintigraphy the 10 mm diameter tablets emptied just before complete emptying of the dextrose drink in two volunteers (Figure 6b). When the results for the beef drink are considered, with EIT the 10 mm tablet emptied after complete emptying of the drink in two volunteers, and the 3 mm tablet emptied after the drink in one volunteer. Using gamma-scintigraphy, the 10 mm tablet emptied before the food in one volunteer, and the 3 mm diameter tablet emptied before the food completely emptied from the stomach in two volunteers. For the solid meal, two 10 mm tablets and one 3 mm tablet emptied before complete emptying measured by EIT (Figure 6a), whereas for the gamma-scintigraphy estimate, one of each diameter tablet emptied before the food was completely emptied (Figure 6b). In no case did the tablet emptying time exceed 6 h, which is contrary to the findings of Kenyon et al (1994), Hardy et al (1987) and Abrahamsson et al (1996).

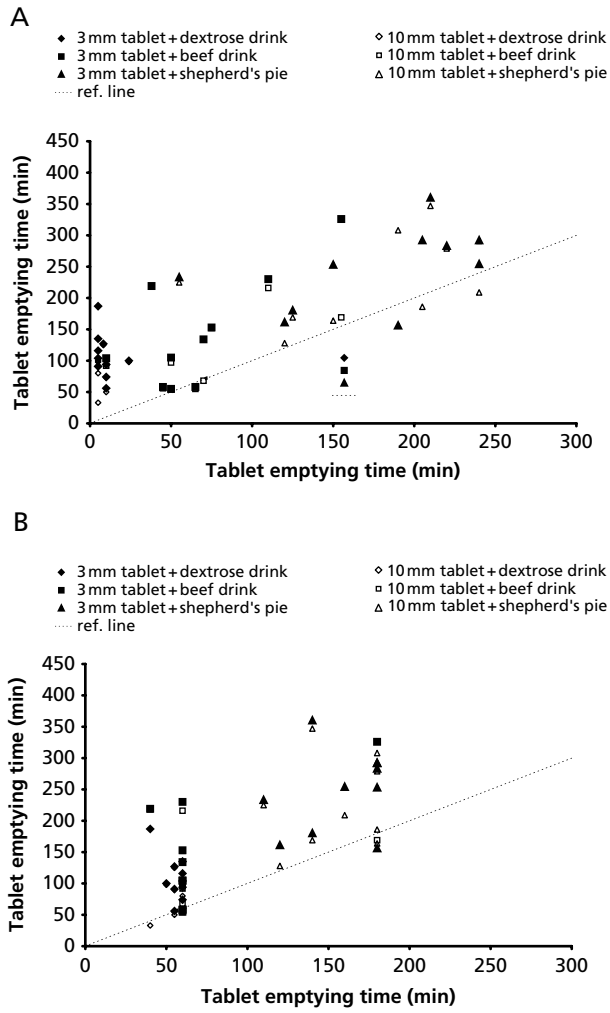

Figure 6 Gastric emptying times for 3 and 10 mm tablets as a function of the time for complete emptying of food (dextrose drink, beef drink, shepherd's pie) determined by electrical impedance tomography (EIT) (A) and gamma-scintigraphy (GS) (B). The dotted line symmetrically dividing the coordinate space indicates the position of data points if there were a perfect correlation between X and Y.

If the median values for the tablet emptying are compared with the median time for complete emptying of the food, results for the two sizes of tablets show the same trend, with the 3 mm tablet emptying after the 10 mm tablet (Table 3). There is considerable variation in the gastric emptying times of both the meals and the tablets. If the results from individual volunteers are considered, with the dextrose and the beef drink, the 10 mm tablet emptied before the 3 mm tablet in eight of the volunteers; the tablets emptied at the same time in the other two volunteers. With the solid meal, the 3 mm tablet emptied after the 10 mm tablet in eight volunteers. In one volunteer the 10 mm tablet emptied after the 3 mm tablet by some considerable margin; in the other volunteer the tablets emptied at the same time. When tested by the Wilcoxon test, the difference between the values for median emptying time of the 3 and 10 mm tablets are statistically different when taken with the dextrose and the beef drink ($Z = -2.812$, $P = 0.005$ for the dextrose; $Z = 2.810$, $P = 0.005$ for the beef drink). When the tablets are taken after the solid meal, however, the difference in median emptying time for the two sized tablets is not significant. A significant difference between either of the liquid meals and the solid meal was confirmed using the Friedman test ($\chi^2 = 12.6$, $P = 0.002$ for 3 mm tablets; $\chi^2 = 12.2$, $P = 0.002$ for 10 mm tablets). The source of the difference is not clear. Lack of accuracy in identifying the exact position of the tablet in the stomach does not help to understand what is actually happening. Emptying of larger tablets before smaller tablets agrees with our previous observations of the effect of size in fasted volunteers (Podczeck et al 1999, 2007a, b). The presence of food will change the dimensions and the shape of the stomach, as well as causing closure of the pyloric sphincter as described in *Gray's Anatomy* (2005). The median emptying times observed here are longer than those for tablets of equivalent size reported previously (Podczeck et al 1999; 2007a, b), which indicates that the 'fed mode' had been induced in the volunteers even by the administration of the liquid drinks. As in the majority of cases, the tablets always empty after the food, whether the food was liquid or solid. Differences in stomach shape and surface texture could be involved, as well as the internal pressure waves. The extended residence time for the tablets taken with the solid meal compared with the liquid meal reflect the lag time before the solid starts to empty. As the food has emptied before the tablets empty, it would appear that the pyloric sphincter must have opened to allow the tablets to empty. It seems unlikely that the pyloric sphincter could differentiate between the 3 mm tablet and the value of 2 mm usually quoted (MacGregor et al 1977; Meyer et al 1981).

Table 3 Mean gastric residence time (MGRT) of the different meals measured with gamma-scintigraphy (GS) and electrical impedance tomography (EIT) and the median gastric emptying time of the 3 mm and 10 mm tablets

	MGRT (min) mean ± s.d.		Tablet emptying time (min), median (IQR)	
	GS	EIT	3 mm	10 mm
Dextrose	21.2 ± 1.9	5.7 ± 0.7	102.0 (42.2)	91.5 (31.2)
Beef drink	24.1 ± 17.4	26.4 ± 8.0	119.5 (163.8)	94.5 (125.0)
Shepherd's pie	53.2 ± 7.2	118.1 ± 28.0	253.5 (116.8)	217.0 (127.5)

IQR, interquartile range.

Evidence of more complex patterns of gastric emptying proposed by Pal et al (2007) will add to the problem of trying to define what is happening, and why the smaller tablets should take longer to empty from the stomach. There is a clear need to identify exactly where the tablets are positioned in the stomach. That the effect is seen when the food is either liquid or solid suggests that the position of the tablets in the stomach may be the controlling feature, rather than the dimensions of the pyloric sphincter. The limitations of resolution of the gamma camera used (10 mm at the body surface) did not allow the exact position of the tablets within the stomach to be determined. It would appear that a more sophisticated technique such as MRI, as described by Schwizer et al (1992, 1993) and Indireshkumar et al (2000), may be required to explain the different emptying patterns of the two sizes of tablets.

Conclusions

The two systems of measuring the gastric emptying of food do not give equivalent results, as they appear to assess different aspects of the process. Whichever method is used to assess the gastric emptying of the food, the results indicate that both sizes of tablet emptied after food had left the stomach. Where the meal was either a dextrose solution or a beef drink, the 10 mm tablet left the stomach before the 3 mm tablet. When tablets were given with solid food, the difference in emptying times was not significant. The difference in gastric emptying times between the two sizes of tablet was far less than that induced by the administration of the solid meal. The extended tablet emptying times previously reported in the literature were not observed here, presumably because we did not allow the volunteers to eat again until the tablets had left the stomach.

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