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Comparative gastrointestinal transit of pellet systems of varying density

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Abstract

Model placebo multiple unit oral dosage forms were prepared by the processes of extrusion and spheronisation. The non-invasive technique of gamma scintigraphy was used to monitor the gastrointestinal transit of these radiolabelled dosage forms. Standard sized units (1.18–1.40 mm) of density 2.0 and 2.4 g cm^{-3} were compared with similarly sized control units of 1.5 g cm^{-3}. Each density was tested separately in eight healthy fasted male subjects. The results showed no differences in the gastrointestinal transit of the three formulations as measured by each of several parameters selected to describe the process. However, the results did reveal some interesting features of the gastric emptying process, and provide further information regarding the critical density at which a prolongation of gastric emptying occurs.

Keywords: Density; Gastric emptying; Gastrointestinal transit; Radiolabeling; Pellet; Technetium-99m; Gamma scintigraphy

1. Introduction

Several technically sophisticated oral sustained release dosage forms have been designed that perform well in vitro, exhibiting well-defined sustained release of drug. However, the performance of such devices in vivo is often limited by the relatively short and variable gastrointestinal transit times in man.

It is commonly accepted that drugs like nutrients are absorbed optimally in the small intestine. Therefore, delaying gastrointestinal transit, specifically delaying gastric emptying, would be advantageous in improving the performance of sustained release formulations.

A number of techniques have been examined to try to achieve prolonged gastric residence. One approach has been modifications of the density of the dosage form. Evidence that an increase in density of the dosage form might be effective in prolonging gastrointestinal transit was first provided by Hoelzel (1930). He measured total gastrointestinal transit of different materials, ranging in density from 0.9 to 10.5 g cm^{-3}, in various animal species including himself. His data indicated that the rate of passage of the various substances was more or less proportional to their

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density, heavier materials passing more slowly than light. Since then, the evidence regarding the effect of density on gastrointestinal transit has tended to be equivocal.

Kirwan and Smith (1974) reported an increase in rate of gastrointestinal transit with increase in specific gravity from 1.1 to 1.35. shortly after, Cummings et al. (1976) administered markers of specific gravities of 1.25 and 1.63, but did not detect any differences in total gastrointestinal transit. Bechgaard and Ladefoged (1978) reported that an increase in density of pellets from 1.0 to 1.6 g cm^{-3} significantly delayed the average gastrointestinal transit time in ileostomy subjects. This was not confirmed by Bogentoft et al. (1982) who examined pellets of density 1.2 and 1.8 g cm^{-3} and found no such differences in transit. Further experiments by Bechgaard et al. (1985) did not reveal any differences in transit between pellets of 0.94 and 1.96 g cm^{-3}.

Kaus et al. (1984a) administered single units of specific gravity 1.03 and 1.61 and did not observe any differences in rates of transit. Similarly, Davis et al. (1986c) and Kaniwa et al. (1988), examined units ranging in density between 0.94 to 1.96 g cm^{-3} and 1.29 to 1.92 g cm^{-3}, respectively, neither group observing any differences in gastric emptying rates. Gruber et al. (1987) examined the gastric emptying of units of a much wider density range (0.5–2.9 g cm^{-3}) in the fasted dog but still concluded that gastric emptying appeared to be independent of density. In contrast, Meyer et al. (1988) examined gastric emptying in humans, and reported delayed emptying of units of density 2.0 g cm^{-3}, relative to those of density 1.0 g cm^{-3}. In 1990, Devereux et al. reported that pellets of density 2.8 g cm^{-3} were significantly prolonged in the human stomach, in both fed and fasted states, relative to control pellets of density 1.5 g cm^{-3}. These latter studies provided more hopeful evidence that gastric emptying might be prolonged by modification of the density of the dosage form, this effect perhaps only becoming apparent at densities greater than had previously been considered.

The purpose of the following study was to examine the gastrointestinal transit of multiple unit formulations of densities 2.0 and 2.4 g cm^{-3}, comparing both with a control formulation of 1.5 g cm^{-3}. The objective was that this range of densities would provide information regarding the critical density at which a prolongation of gastric residence could be achieved.

The multiple unit formulations were administered to fasted subjects, as food is well known to delay gastric emptying of dosage forms (Davis et al., 1986a; Sangekar et al., 1987). A dosage form exhibiting extended gastric residence in the fasted state would have to resist the strong propulsive effects of the phase III housekeeper wave.

Each subject acted as his own control and received all three dosage forms, thereby removing inter-individual variability.

2. Materials and methods

Gastrointestinal transit of the three multiple unit dosage forms was monitored by radiolabelling the pellets with the gamma emitting nuclide Technetium-99m (^{99m}Tc) and visualising externally using a double-headed gamma camera (Siemens 'Rota' gamma camera).

Three batches of pellets were prepared, each 1.2–1.4 mm in size and having final densities, after film coating and radiolabelling, of 1.5, 2.0 and 2.4 g cm^{-3}, as measured by air comparison pycnometry. The encapsulated pellets had an activity of 3.7 MBq at the time of administration.

Pellets were prepared by the pharmaceutical processes of extrusion and spheronisation from formulations containing microcrystalline cellulose (Avicel PH101, FMC, Philadelphia, U.S.A.) and barium sulphate (East Anglia Chemicals, Suffolk) in appropriate proportions so as to effect pellets of the required densities. The stability of the radiolabel on the pellets was achieved by the incorporation of 5% w/w of an anionic exchange resin (Amberlite CG400(Cl), Aldrich Chemical Co., Dorset) into the core formulation. The pellet cores were film coated with ethylcellulose N50 (Hercules, DE, U.S.A.) containing 30% polyethylene glycol 4000 (Hoechst, Frankfurt) to provide a final dosage form that accurately modelled a standard pharmaceutical formulation.

The pellets were radiolabelled with ^{99m}Tc, by

soaking for 2 h in a 2 ml solution of sodium pertechnetate. The labelling was achieved by the radionuclide permeating the film coat and strongly binding to the ion exchange resin. After the labelling period the pellets were rinsed to remove any unbound pertechnetate and dried overnight before filling into size 0 hard gelatin capsules.

The stability of the radiolabel on the pellets was confirmed by an in vitro test. Encapsulated, radiolabelled pellets were exposed to simulated gastric fluid (USP XXII 1990, omitting pepsin) for 2 h (the estimated likely residence time in the stomach), after which time the supernatant was examined for released ^{99m}Tc. The pellets were then transferred to simulated intestinal fluid (USP XXII 1990, omitting pancreatin) for a total of 22 h and the supernatant assessed periodically for released radioactivity. Total release of radioactivity over 24 h was $< 1\%$ for each batch of pellets. The radiolabelled pellets were thus considered satisfactory for in vivo administration.

Eight male subjects (age range 22–51 years, median 26 years; weight range 59–76 kg, median 66 kg) participated in this study, after providing written informed consent. Each subject declared himself to be healthy, was a non-smoker, was taking no medication, and had no history of gastrointestinal disorders. The study protocol was approved by University College Hospital Ethics Committee. Three days of study were completed by each subject, the density of pellets within the capsule varying on each administration. The order of administration was randomly assigned and was not known to the subject.

On the day of the study, the subject presented, having fasted from midnight. The subject was seated comfortably in an upright position, between the two detector heads of the gamma camera (Siemens Rota). A sealed point source of 0.5 MBq ^{99m}Tc was taped to the abdominal skin at the position of the right lower costal margin. This allowed accurate repositioning of the subject between images, and also acted as an anatomical reference marker.

At 9 a.m. ($t = 0$) the subject swallowed the capsule with 200 ml orange juice and the first image acquisition commenced. For the first 90 min, images of 60 s duration were acquired continuously and simultaneously from anterior and posterior detectors. Thereafter, images were acquired at 5–10 min, or more frequently if necessary. The objective was to maximise the information collected over the critical period of gastric emptying. Subjects were provided with coffee (200 ml) after 90 min and a standard lunch at 210 min, comprising a Macdonald's 'Quarterpounder' hamburger, french fries, apple and coffee. Imaging was continued after lunch at approx. 0.5 h intervals as appropriate. The acquisition time was increased to 120 s to compensate for the radioactive decay of ^{99m}Tc. Additional refreshments were provided at $t = 390$ min (200 ml tea) and, if necessary, a pizza supper at $t = 540$ min.

Acquisition and storage of images were continued in this way until more than half of the radiolabelled dosage form was judged to have entered the large intestine, or until it was unreasonable to detain the subject any longer. Once all the transit data had been collected, the subject swallowed 200 ml orange juice labelled with 0.5 MBq ^{99m}Tc-diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA, Malinckrodt Diagnostica, The Netherlands). A 180 s image was collected. This procedure enabled the stomach outline to be identified.

2.1. Image analysis

The position of the stomach was identified by reference to the final image of the sequence, acquired after ingestion of radiolabelled orange juice. A gastric region of interest was delineated on the screen with the light pen. The entire sequence of images was then replayed to confirm and fine-tune this gastric region of interest. The position of the caecum was well-defined in the latter images as a result of concentration of the radiolabelled preparation within this organ. This enabled an outline of the caecum to be delineated on the computer screen.

A double-headed gamma camera is of particular value in studies of gastric emptying as demonstrated by the physiology of this process. The normal stomach is not parallel to the abdominal wall, the corpus lying in a more posterior position

than the pylorus. As radiolabelled gastric contents move from the corpus into the antral and pyloric regions, as occurs prior to emptying, they also move anteriorly. Since the degree of attenuation of a point source of radioactivity in the body is dependent on the depth of that source within the body, the observed count rate in the anterior projection increases. At the same time the observed count rate in the posterior projection decreases. It has long been known (Evans, 1937) that this feature of gastric emptying studies can be compensated for by calculating the geometric mean of net counts from anterior and posterior views. When a double-headed gamma camera system is not available, investigators compensate by collecting sequential anterior and posterior images which, for analytical purposes, are treated as occurring simultaneously (Davis et al., 1984a,b, 1986b, 1987; Christensen et al., 1985; Moore et al., 1985). This necessitates continually moving and repositioning the subject for each measurement. This is inconvenient to both the subject and the investigator, and does not lend itself to frequent data sampling. Consequently, important events in the gastric emptying process may be missed or at best measured inaccurately. The 'Rota' camera collects both anterior and posterior images simultaneously making calculation of the geometric mean simple and routine.

The counts recorded for each area of interest by each detector were calculated by the computer for each image. These values were normalised for a constant counting interval and corrected for background count rates. The background corrections were achieved by subtracting, from each pixel in the area of interest, the mean count rate per pixel from a region of interest defined at the edge of each image. The geometric mean count was calculated from these net counts and corrected for radioactive decay. The geometric mean counts from both the stomach and caecum regions of interest were expressed as percentages of the total counts recorded in the first frame attributable to the administered dosage form.

2.2. Data processing

Gastric emptying of multiple unit formulations is complex and very variable. Hunter et al. (1983) observed at least five different patterns of emptying of encapsulated formulations. It is therefore not possible to concisely describe the emptying process by fitting a universal mathematical curve to the data points. A frequent approach has been to average gastric emptying data across subjects for each time point and to plot the resulting average curve (Davis et al., 1984b, 1987; Christensen et al., 1985; Ollerenshaw et al., 1987; Urbain et al., 1989). However, the shape of the mean curve need not be at all typical of the shapes of the individual curves and important features of the original emptying curves may be hidden. The only way to display, examine and understand the details of the emptying process is to plot the emptying curves separately for each individual (Elashoff et al., 1982). An objective, quantitative comparison is preferable, but difficult, since no single parameter is sufficiently flexible to provide adequate descriptions of the wide variety of emptying patterns that might be encountered. A best approximation is to focus on a number of important features of the total curve likely to change with different emptying patterns. Statistical tests can then be performed on these numerical values.

The gastric emptying and caecal arrival curves were plotted for each individual and for each dosage form, allowing qualitative differences to be identified. A number of parameters from different parts of the emptying curve were selected as indicative measures of the emptying process. The first parameter was the time until the start of gastric emptying (lag time). This was defined as the time of the last image when all the detectable activity, and therefore all the pellets, remained within the stomach region of interest. The $t_{50\%}$ value for gastric emptying (G_{50}) was interpolated from the emptying curve and represented the time at which 50% of the activity had passed out of the stomach. Although this parameter is commonly used to describe gastric emptying of dosage forms, it makes limited use of the wealth of data collected. In order to utilise a greater proportion of the data points, the area under the emptying curve (AUC) was computed. This value was normalised for the variation observed in the quantification of the gastric emptying curves over the lag

period (oscillations observed in Fig. 1). The value for AUC is proportional to the mean residence time of the dosage form within the stomach. This method was found by Dugas et al. (1982), Grimes and Goddard (1977) and Gulenchyn et al. (1987) to provide a better estimate of the emptying process. Arrival of pellets at the caecum was described by a $t_{50\%}$ value for caecal arrival (C_{50}). This represented the time, from ingestion, until 50% of the pellets had entered the caecum and was obtained by graphic interpolation. The final parameter of interest was the value for small intestinal residence time (SIRT). This was obtained by the difference between the $t_{50\%}$ values for caecal arrival and gastric emptying (i.e., $C_{50} - G_{50}$).

2.3. Statistical analysis

The effect of each of the three formulations on the different aspects of gastrointestinal transit was examined by performing a two-way analysis of variance, since the data were classified in two ways: by dosage form and by individual. An alternative would have been to perform separate t-tests, taking two samples at a time. Not only would this approach have been time-consuming but, more importantly, performing a large number of t-tests increases the risk of obtaining a statistically significant result by chance alone.

The basis of analysis of variance is to pool all the data to give a single, much better estimate of variance, with a larger number of degrees of freedom. The null hypothesis tested was that the means recorded were different samples of the same population. The size of the variance, between each treatment, was compared to the overall variance, to test the null hypothesis.

3. Results and discussion

Curves for gastric emptying and caecal arrival were plotted separately for each individual. The majority of emptying curves showed a distinct plateau phase, corresponding to the lag period, followed by very rapid emptying of the pellets. This feature of the emptying process could be identified because of the very frequent data sampling and was similar to that observed by Devereux et al. (1990). The gastric emptying and caecal arrival profiles for each of the three formulations are shown in Fig. 1 for subject 3. This individual demonstrated three distinct patterns of pellet emptying. The lightest pellets showed the typical pattern of rapid emptying following the lag phase. Pellets of intermediate density started to empty from the stomach at about 200 min. Emptying was initially rapid, but was soon interrupted by the ingestion of lunch at 210 min. Thereafter, gastric emptying was slowed down by the presence of food within the stomach. Emptying of the heaviest pellets followed a two-stage process. Approximately one-third of the pellets emptied rapidly after an initial lag period, the emptying then being delayed for a second more prolonged lag period. The remainder of the pellets then emptied rapidly and completely. The three different patterns of emptying observed in this one individual indicate how inappropriate it

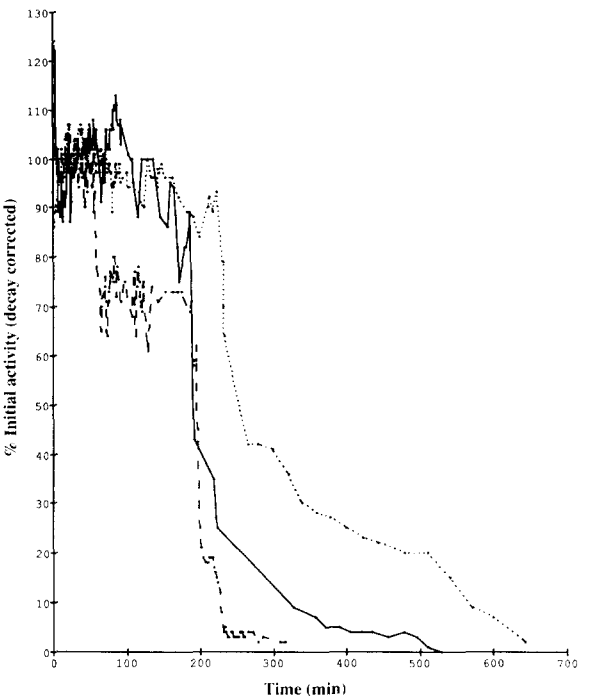

Fig. 1. Gastric emptying of pellets in subject 3. Gastric emptying: (– · – · –) $d = 1.5$ g/cm^3, (· · · ● · · ·) $d = 2.0$ g/cm^3, (— · —) $d = 2.4$ g/cm^3.

would be to attempt to fit a universal curve to the emptying data.

The rapid emptying of the bulk of the pellets was presumably associated with phase III of the interdigestive motor complex. On those occasions when emptying of pellets occurred just prior to lunch, subsequent ingestion of the meal appeared to be very effective in slowing further gastric emptying of pellets. Presumably, the interdigestive motor complex was interrupted by the ingestion of lunch, preventing the remainder of the pellets leaving the stomach by way of phase III contractions. Emptying was not stopped completely but thereafter occurred more slowly as a first-order process, over a prolonged period. It appeared that pellets were emptying with the meal and were not being selectively retained by the pylorus.

Gastric emptying of pellets of density 2.0 g cm^{-3} in subject 4 can be observed visually in Fig. 2 and 3. The differences between the four images taken at 1 min intervals demonstrate the rapidity of the gastric emptying process and show how frequent imaging is essential to accurately and precisely describe the process.

The individual results for the gastrointestinal transit parameters are shown in Tables 1 and 2, and summarised in Table 3.

The data indicated a very wide spread of recorded lag times, ranging from 0 to 208 min. Administration of the heaviest pellets to subject 7 resulted in a lag time of 0 min. The sequence of images revealed that, by the start of the second frame ($t = 1$ min), the dosage form had completely left the stomach. A probable explanation is that, at the time of dosing, the fasted subject was in phase III of the interdigestive cycle. One of the intense bursts of peristaltic contractions, which occur approximately every 20 s during this period must have swept the dosage form out of the stomach as soon as it was swallowed. The rapid simultaneous ingestion of the orange juice may have assisted the flushing of the capsule through the pylorus. The pellets would have left

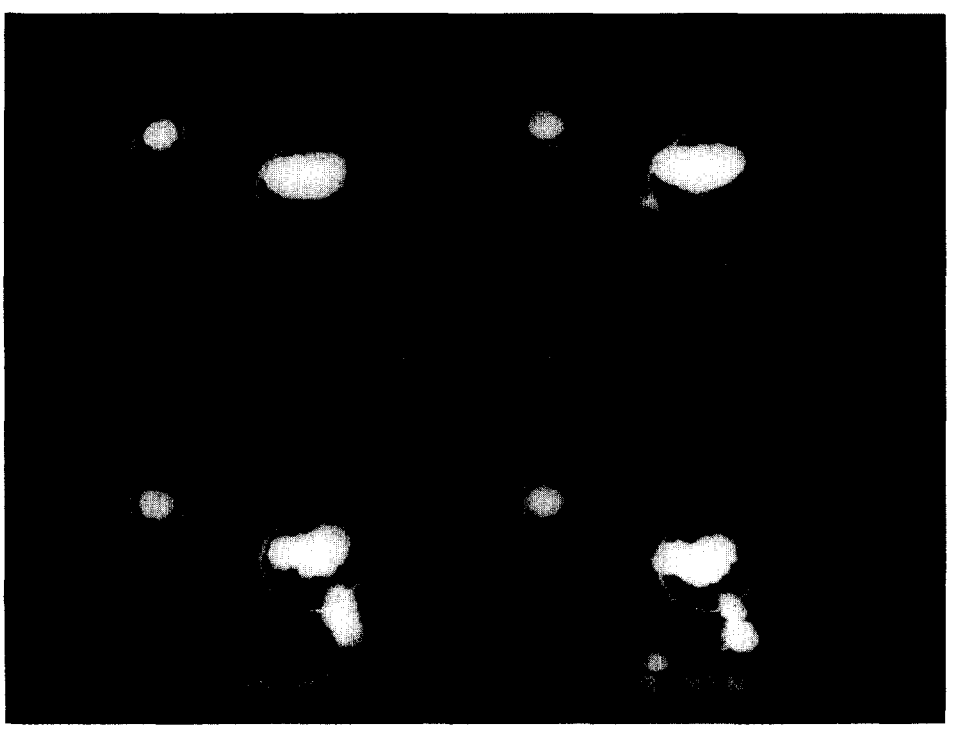

Fig. 2. Commencement of gastric emptying of pellets of density 2.0 g cm^{-3}.

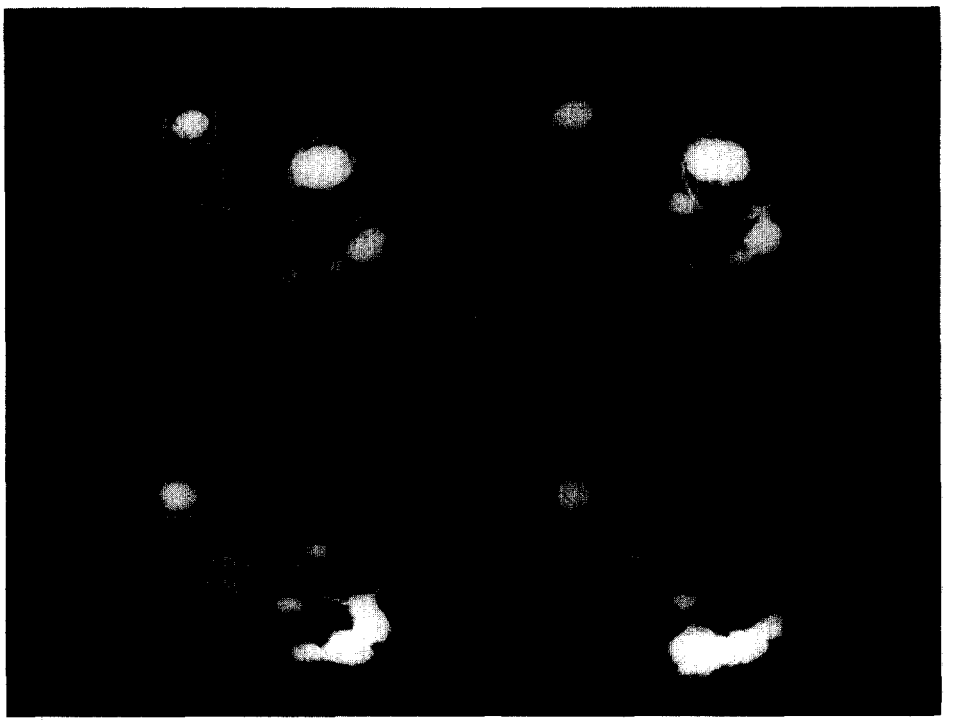

Fig. 3. Gastric emptying of pellets of density 2.0 g cm^{-3}.

the stomach still encapsulated, as there would have been insufficient time for dissolution of the gelatin.

Overall, there were no significant differences in any of the emptying parameters attributable to pellet density. However, there were significant differences between individuals for two of the transit parameters (G_{50} and AUC). Intersubject variability has also been noted by others (Heading et al., 1976; Kaus et al., 1984b; Bechgaard et al., 1985; Christensen et al., 1985). For this reason the study was of the paired design, each

Table 1
Individual and summarised gastric emptying parameters

Subject	Lag (min)			G_{50} (min)			AUC		
	1.5 g cm^{-3}	2.0 g cm^{-3}	2.4 g cm^{-3}	1.5 g cm^{-3}	2.0 g cm^{-3}	2.4 g cm^{-3}	1.5 g cm^{-3}	2.0 g cm^{-3}	2.4 g cm^{-3}
1	73	94	54	87	101	85	13308	10831	17681
2	175	19	187	221	196	213	26518	17681	22951
3	94	200	57	190	254	196	19919	33150	15754
4	73	66	93	101	79	126	14008	7579	25963
5	208	192	136	477	261	279	41214	32736	32626
6	87	36	81	124	178	202	15173	16973	17571
7	21	93	0	178	219	1	14635	20619	48
8	91	111	171	98	201	238	11052	19184	19661
Mean	103	101	97	185	186	168	19478	19844	17842
SD	60	66	64	128	66	91	10023	9172	9439
Overall mean		101			179			19055	

Table 2
Individual and summarised gastrointestinal transit parameters

Subject	SIRT (min)			C_{50} (min)		
	1.5 g cm^{-3}	2.0 g cm^{-3}	2.4 g cm^{-3}	1.5 g cm^{-3}	2.0 g cm^{-3}	2.4 g cm^{-3}
1	321	367	101	408	468	186
2	379	105	255	600	301	468
3	353	378	262	543	632	458
4	233	242	280	334	321	406
5	300 [a]	275	250	> 540	536	529
6	246	221 [a]	144	370	404 [a]	346
7	190	241	149	368	460	150
8	148	278	188	246	415	387
Mean	271	263	204	426	442	366
SD	81	86	67	122	109	135
Overall mean		246			412	

[a] Estimated value.

subject acting as his own control. This procedure is essential when the sample sizes are small and when the differences between test preparations are also likely to be small.

Considerable work has been performed to examine the effect of size on gastric emptying. Work in dogs by Meyer et al. (1979) demonstrated that the normal canine stomach would only allow passage of meat in the form of particles smaller than 2 mm, this discriminatory feature reliant on a functioning antrum. Further experiments by Meyer et al. (1985) led to the conclusion that non-digestible spheres will empty promptly and rapidly from the canine stomach if they are small enough, the critical size declared as approx. 1.6 mm. Critical size experiments were performed in humans postprandially, and resulted in a similar upper size limit (Meyer et al., 1988). Davis et al. (1986a) examined the gastric emptying of spheres ranging in size from 0.5 to 2 mm, and concluded that all spheres < 2 mm emptied from the stomach quite rapidly, this process not greatly affected by the digestive state of the individual. In this study it was quite clear that the pellets, which are smaller than 2 mm, did not leave the stomach with the liquid phase. Devereux (1987) measured the rate of emptying of orange juice from the fasted stomach and observed a mean G_{50} value for liquid emptying of 24 min. On average, these pellets did not start to leave the stomach until after 101 min, by which time the emptying of the orange juice would have been complete. Emptying of the pellets appeared to occur quite independently of liquid emptying.

Table 3
Summary analysis of variance table

Source of variation	F					
	df	Lag	G_{50}	AUC	SIRT	C_{50}
Between subjects	7	1.97	3.66 [a]	3.81 [a]	1.04	2.14
Between pellets	2	0.02	0.17	1.83	1.80	1.18
Residual [b]	14					

[a] Significant at 5% level.
[b] Residual degrees of freedom reduced by 2 to 12 for SIRT data, and by 1 to 13 for C_{50} data in accordance with the method for estimating missing data (Snedecor and Cochran, 1980).

Although these pellets are theoretically small enough to be emptied through the pylorus at times other than with the 'housekeeper' wave, there seems to be an additional requirement for emptying. This is presumably provision of some mechanism by which the solid particles can access the pyloric opening, since it is at the side of the stomach rather than at the base. In the digestive phase the pellets might be propelled into the antropyloric region by gastric contractions. In the absence of any contractile activity, it appears that the solid requires to be suspended in the liquid, so that it can reach the pylorus. In these studies,

neither mechanism of emptying was possible. The subjects were studied in the fasted state, and even the lightest pellets (1.5 g cm^{-3}) were significantly heavier than the liquid phase ($\sim$ 1.0 g cm^{-3}). The images confirmed that once the gelatin capsule had dissolved, the pellets sank to the bottom of the stomach before they could flow with the liquid into the antropyloric region. No emptying of pellets was observed until, presumably, phase III of the interdigestive cycle commenced, this accounting for the existence of the lag phase.

From the caecal arrival curves, and as was evident from the images (Fig. 4), arrival of pellets in the caecum seemed to occur in a bolus fashion, subsequent to a period of stasis at the oral side of the ileocaecal junction. On two occasions collection of caecal arrival data was incomplete. With subject 5, the last recorded time point of 540 min could be meaningfully used as an estimate for C_{50}, albeit an underestimate. However, this still left two missing values for SIRT and one missing value for C_{50}. Since incomplete data can bias results, especially in studies of small sample size, the three missing values were estimated according to the method of Snedecor and Cochran (1980). An analysis of variance of the small intestinal residence and caecal arrival data, after replacing the missing values with estimated values, found no significant differences in either parameter either by pellet density, or by subject.

4. Conclusion

The results of these studies have indicated that, at densities up to 2.4 g cm^{-3}, there is no difference in gastrointestinal transit of pellets of size 1.2–1.4 mm, to that of a standard control multiple unit formulation of density 1.5 g cm^{-3}. Devereux et al. (1990) compared a multiple unit formulation of density 2.8 g cm^{-3}, with a control formulation of 1.5 g cm^{-3}, and found significantly delayed gastric emptying of the heavier formulation in both fed and fasted conditions. These studies were performed under identical condi-

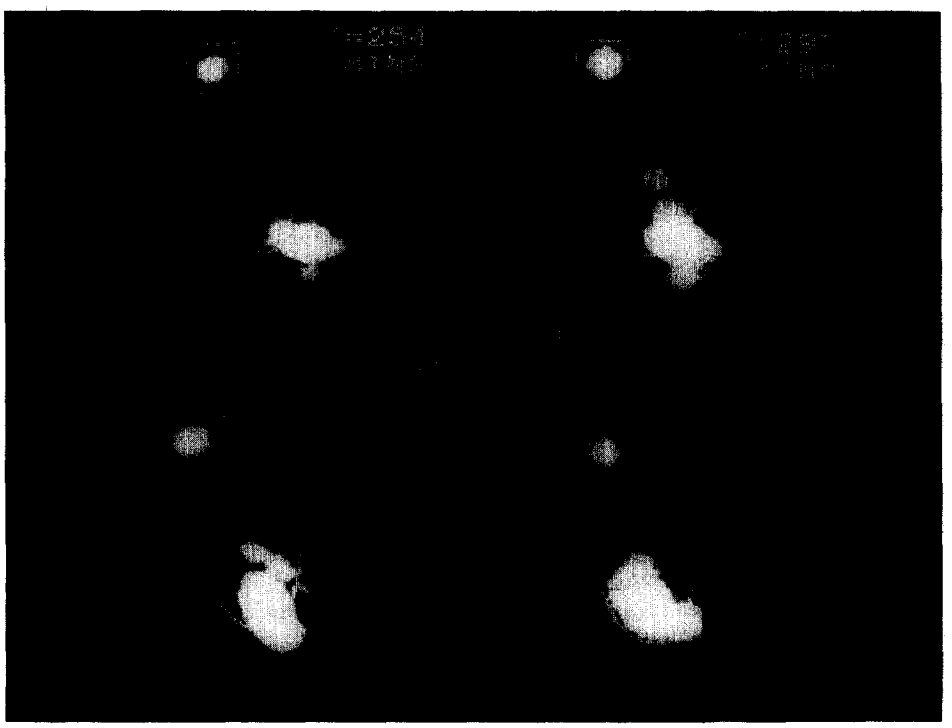

Fig. 4. Caecal arrival of pellets of density 2.0 g cm^{-3}.

tions to those carried out by Devereux et al. (1990), and since no prolongation or delay of gastric emptying was observed with these dosage forms, it appears likely that the critical density to achieve prolonged gastric residence lies between 2.4 and 2.8 g cm^{-3}.

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