International Journal of Pharmaceutics, 100 (1993) 81–92

IJP 03282

Gastrointestinal transit of pellets of differing size and density

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(Received 16 January 1993)
(Modified version received 25 March 1993)
(Accepted 16 April 1993)

Key words: Extrusion/spheronisation; Gamma scintigraphy; Gastrointestinal transit; Pellet; Density; Pellet size

Summary

The gastrointestinal transit of four multiple unit pellet dosage forms of two sizes 0.5 and 4.75 mm and two densities 1.5 and 2.6 g cm^{-3} was examined by gamma scintigraphy in eight healthy fasted subjects. The pellets were prepared by the processes of extrusion and spheronisation and radiolabelled with ^{99m}Tc or ^{111}In. Small pellets of normal and high density were examined on one occasion and large pellets of normal and high density on another. The small and large pellet data from each administration were analysed separately, and then pooled to determine the overall effects of size and density on gastrointestinal transit. A distinct lag phase before gastric emptying commenced was observed for all pellets. The onset of emptying was not affected by size or density. Thereafter gastrointestinal transit did appear to be prolonged with an increase in density. This effect was more clearly demonstrated by the smaller pellets. Small pellet data and the pooled data indicated that an increase in density delayed gastric emptying and prolonged small intestinal residence time ($p < 0.05$). The large pellet data alone, also indicated that the increase in density caused a delay in gastric emptying ($p < 0.05$) but the prolongation of small intestinal residence time was not significant. Gastric emptying of the pellets was not affected by their size, although small intestinal residence time was prolonged by the large pellets ($p < 0.05$). These results and those previously reported by the authors (Clarke et al., *Int. J. Pharm.*, (1993 in press) suggest that there may be a threshold density, of the order of 2.4–2.6 g cm^{-3}, above which gastric emptying is prolonged. The delayed gastric emptying and prolonged small intestinal residence time have important implications for the rational design of sustained release oral dosage forms.

Introduction

Devereux et al. (1990) have reported that 1 mm pellets of density 2.8 g cm^{-3} took longer to empty from the stomach than those of a more usual density of 1.5 g cm^{-3}, when given to both fasted and fed volunteers. That the density must exceed 2.4 g cm^{-3} has recently been established in a previous paper (Clarke et al., 1993). A further factor involved in the process of emptying is the size of the pellets. Conventional pellet formulations are usually of a diameter in the order of 1.0–1.4 mm, and there are no studies that examine the influence of size of such formulations on gastrointestinal transit. There is, however, the often quoted concept that small pellets will empty

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like a liquid, although there is no clear evidence as to what this threshold size actually is. The work of Devereux (1987) clearly established that the threshold size must be below 1 mm, for with none of the 1 mm formulations tested did emptying of these pellets correspond to a liquid. There was always a significant lag time, even in fasted volunteers. Thus there is a need to establish whether pellets of diameter less than 1 mm will behave as a liquid. By careful experimentation Clarke (1989) established that 0.5 mm pellets could be produced by extrusion spheronisation.

At the other end of the scale, the upper limit of pellet size that can be manufactured would seem to be the limiting factor in the use of such preparations in practice. There is little information in the literature on this limit, although the early work of Reynolds (1970) does illustrate that pellets larger than 1 mm in diameter can be prepared. Clarke (1989) established that pellets approaching 5 mm diameter could be manufactured reproducibly, and hence it is possible to compare such a formulation with the 0.5 mm diameter pellets. Producing these dimensions of pellets at two densities allows comparison of the gastrointestinal transit of both pellet size and density in the one experimental design.

Materials and Methods

Eight male subjects (age range 21–53 years, median 24 years, weight range 57–94 kg, median 67 kg) participated in this study after providing informed written consent. Each subject declared himself to be healthy, was taking no medication and had no history of gastrointestinal disorders. All subjects were non-smokers, with the exception of subjects B and E, who typically smoked 15 and 5 cigarettes per day, respectively. Neither had smoked since midnight on the days of study and they were not permitted to smoke during the course of the study. The study protocol was approved by University College Hospital Ethics Committee. 2 days of study were completed by each subject. On each occasion the subject swallowed two identical capsules, each containing a mixture of small or large pellets of normal and high densities. The pellets will be given the designation of light (1.5 g cm^{-3}) and heavy (2.6 g cm^{-3}) to identify the two density levels. The order of administration was randomised and was not known to the subject.

On the day of study the subject presented having fasted from midnight. He was seated comfortably between the two detector heads of a gamma camera (Siemens Rota), each fitted with medium energy collimators, and a sealed source of ^{99m}Tc was taped to the skin at the right lower costal margin to act as an anatomical reference. At 9 a.m., the subject swallowed 50 ml orange juice followed by the two capsules with the remaining 150 ml of the juice and the first acquisition of 60 s was commenced. Imaging and data collection were performed continuously for the first 90 min and at 5–10 min intervals thereafter.

Imaging was simultaneous from both detectors, but since the camera console possessed only two analyser modules, imaging was performed alternately over lower and upper energy windows (15% window centred at 140 keV, and 48% window centred at 208 keV, respectively). The time and energy window were noted for each frame.

Refreshments were provided at set times (Clarke et al., 1993) until at least 50% of each labelled dosage form was judged to have entered the large intestine.

Image analysis

A region of interest was drawn around the anatomical marker on the first frame and the subsequent images checked for subject movement. Since the marker was a ^{99m}Tc source of activity, its presence was not visible on the ^{111}In images. Consequently, if excessive movement was observed on a ^{99m}Tc image, both that image and the corresponding ^{111}In image were ignored during subsequent analysis. In addition, the assumption was made that if the patient position was satisfactory on a ^{99m}Tc image, the corresponding ^{111}In image was also considered satisfactory.

Identification of the gastric region of interest was established by reference to the complete set of images. The position of the caecum was identified by reference to the images collected towards the end of the study, in which there was a well-

defined concentration of radiolabelled preparation within this organ.

The counts recorded for each area of interest by each detector were calculated by the computer for each image. These values were corrected for a constant counting interval and for background count rates. ^{99m}Tc counts were also corrected for ^{111}In down-scatter. The geometric mean counts were calculated from these net counts, corrected for radioactive decay and expressed as a percentage of initial total activity.

Data processing

Gastric emptying and caecal arrival curves were plotted for each individual and for each dosage form. This permitted any qualitative differences in the gastrointestinal handling of the dosage forms to be identified.

The following parameters were selected from the emptying curves and caecal arrival curves as representative indicators of the processes; the time for 50% of the pellets to leave the stomach (G50), normalised area under the curve as a further representation of gastric residence time (AUC), the time for 50% of the pellets to enter the caecum (C50) and the difference between C50 and G50 as a measure of small intestinal residence time (SIRT). These values were determined by the methods described by Clarke et al. (1993).

Statistical analysis

The data from this study were in the form of four observations from each subject. Since small, light and heavy pellets were examined on one occasion and large, light and heavy pellets on a different occasion, the measurements of gastrointestinal transit between the different densities of a specified size are more closely comparable than the corresponding pooled measurements between the different densities across the different sizes. Therefore, the preliminary analysis involved performing separate paired *t*-tests on the small and large pellet data, before pooling the data on the basis of size and density. The pooled data could then be analysed by a factorial analysis of variance. This gives a single much better estimate of variance, with a larger number of degrees of freedom.

Results

Curves for gastric emptying and caecal arrival of pellets were plotted separately for each individual. The general pattern of gastric emptying was similar in almost all subjects and for all pellets and consisted of rapid gastric emptying subsequent to a lag phase of variable duration. This pattern is demonstrated in Figs 1 and 2 which show the gastric emptying and caecal arrival of small and large pellets, respectively, in subject G. Pellet entry into the caecum tended to occur in a bolus fashion.

A comparison of gastrointestinal transit of small light and heavy pellets is shown in Figs 3–8 for subject H. Gastric emptying of both light and heavy pellets commenced at the same time, although the 50% emptying time for light pellets was 192 min as opposed to 237 min for the heavy pellets. Figs 7 and 8 illustrate a situation where caecal arrival of small, heavy pellets commenced before gastric emptying of these pellets was complete.

Gastrointestinal transit of large light and heavy pellets is summarised in Figs 9–14 for subject H. The first images in Figs 9 and 10, show the dosage form located towards the top of the stomach, floating on top of the simultaneously ingested orange juice. Once the capsule shell had dissolved, the pellets, being denser than the gastric contents, descend to the base of the stomach. However, at least one of the light pellets remained high up in the body of the stomach for at least 55 min. The reason for this was unclear, although the light pellet may have become adhered to the gastrointestinal mucosa in this region. The light pellets started to leave the stomach before the heavy pellets and also reached the caecum in advance of the heavy pellets. The latter images, when one half-life of ^{99m}Tc had elapsed, indicate the more pronounced effect of ^{111}In down-scatter into the ^{99m}Tc window. This is demonstrated as a small but detectable area of radioactivity within the caecum. Quantitative

analysis of the images revealed that this radioactivity was attributable to light ^{111}In pellets already within the caecum, and not to ^{99m}Tc-labelled heavy pellets.

The numerical results for the gastrointestinal transit parameters are shown and summarised in Tables 1–4. The factorial analysis of variance revealed significant differences ($p < 0.01$) be-

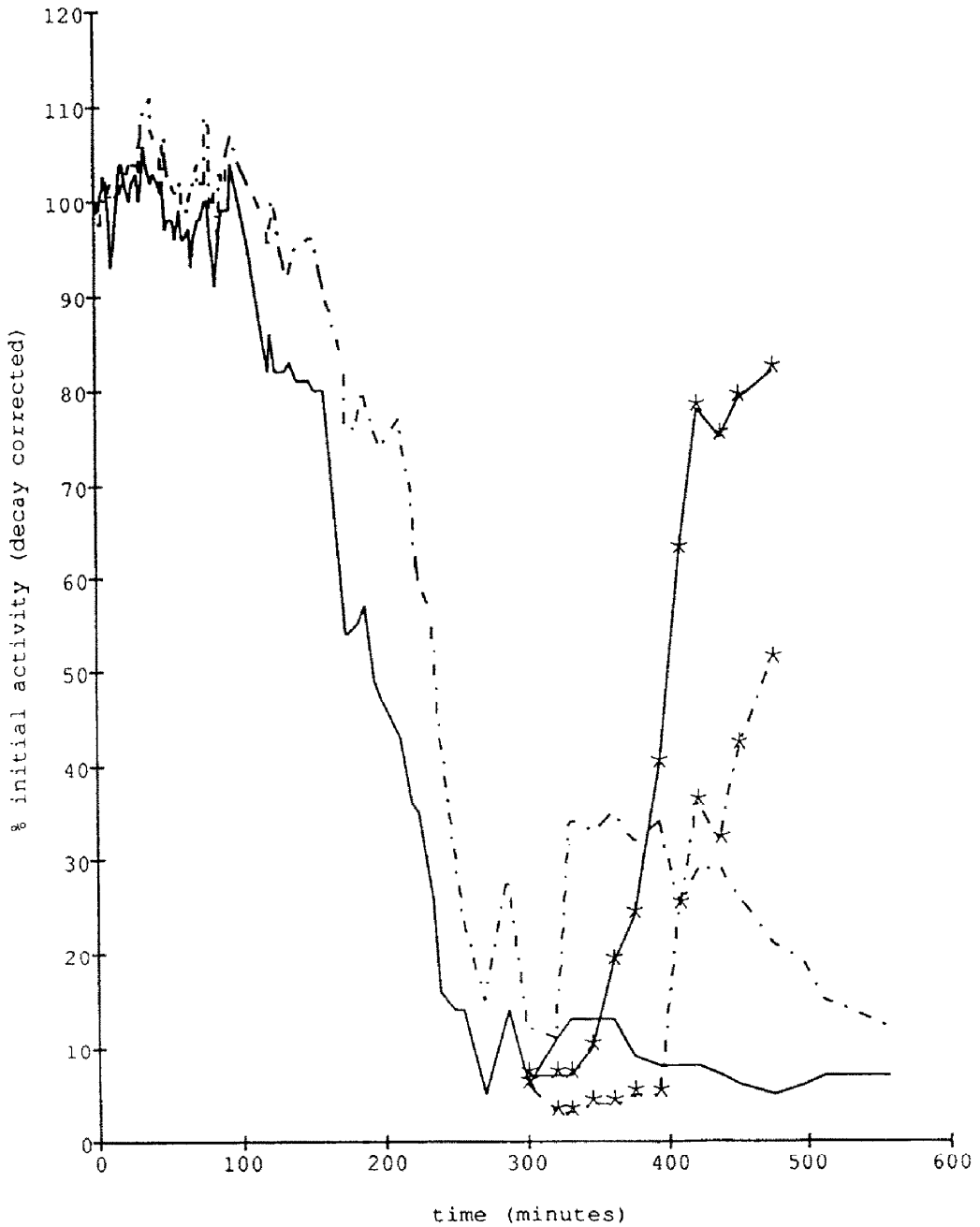


Fig. 1. Gastric emptying and caecal arrival of small pellets in subject G. (———) Gastric emptying of light pellets; (- - -) gastric emptying of heavy pellets; (— * —) caecum arrival of light pellets; (- - * - -) caecum arrival of heavy pellets.

tween subjects for all measurements of gastrointestinal transit studied (Table 4). This reaffirms the importance of using each subject as their own control. The analysis indicated that there was no interaction between the effects of pellet density and size and therefore, these parameters could be analysed independently.

A paired *t*-test performed on the 50% empty-

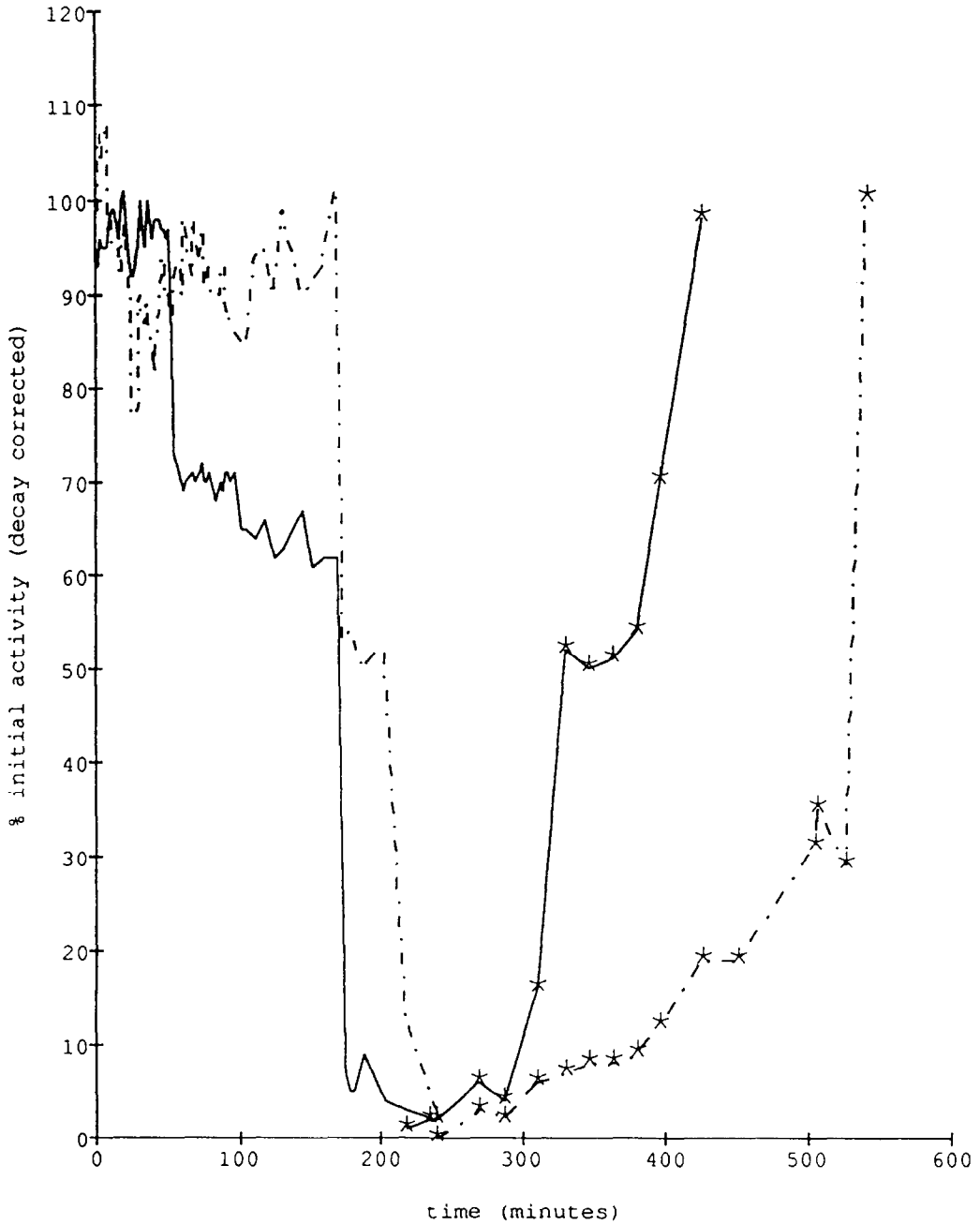
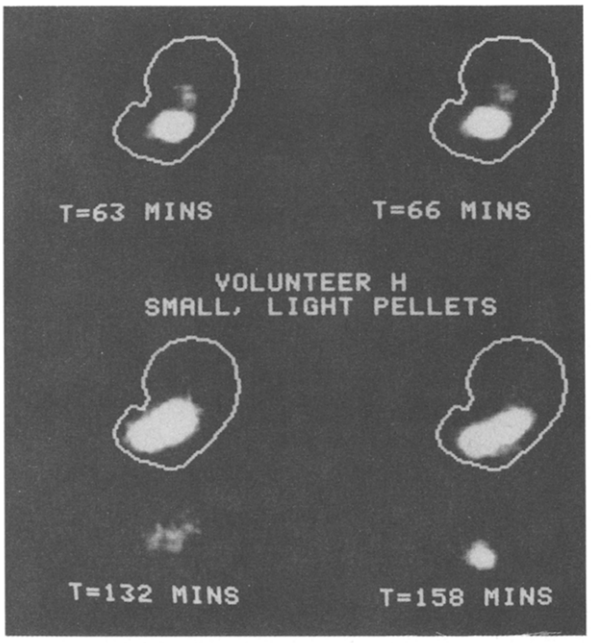


Fig. 2. Gastric emptying and caecal arrival of large pellets in subject G. (———) Gastric emptying of light pellets; (- - -) gastric emptying of heavy pellets; (— * —) caecum arrival of light pellets; (- - * - -) caecum arrival of heavy pellets.



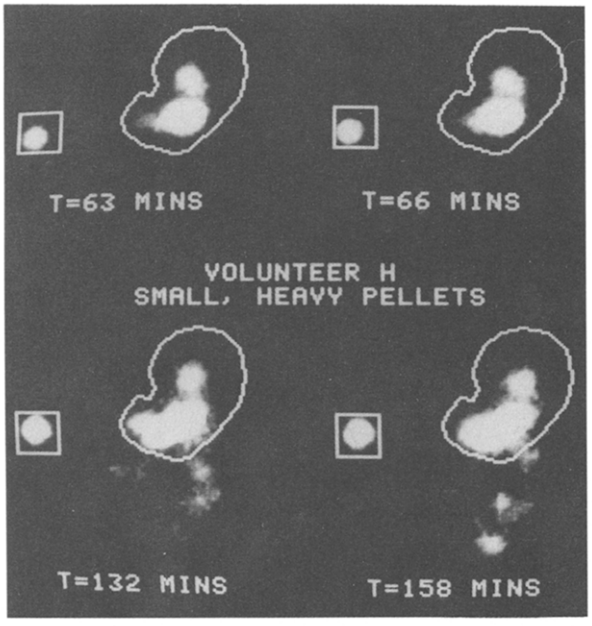
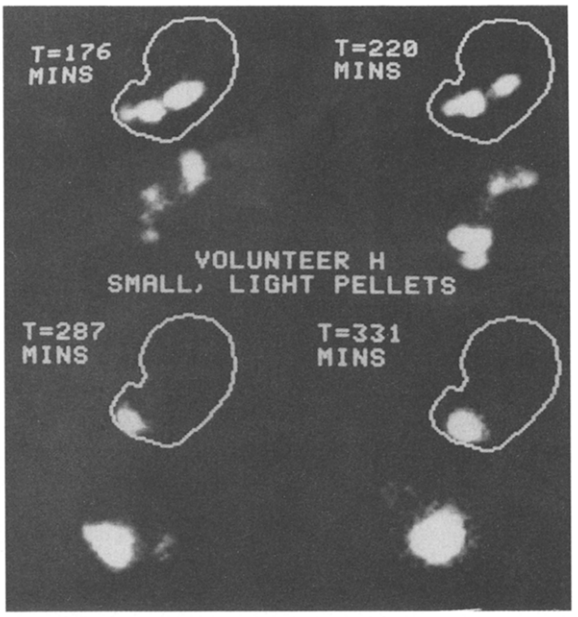


Fig. 3. Commencement of gastric emptying of small, light pellets.

Fig. 4. Commencement of gastric emptying of small, heavy pellets.



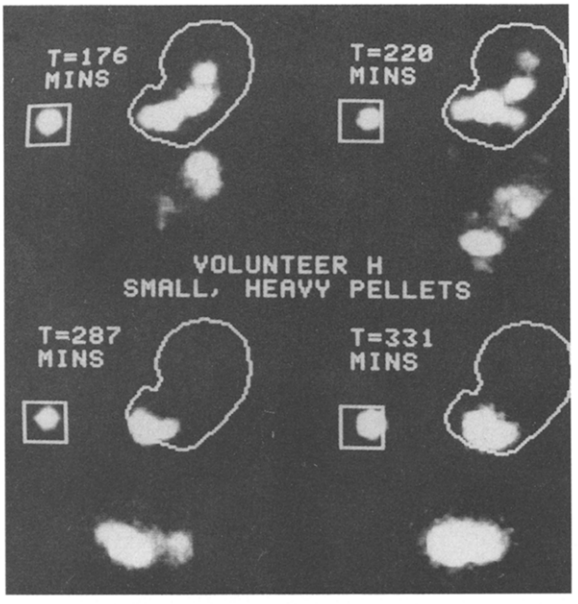
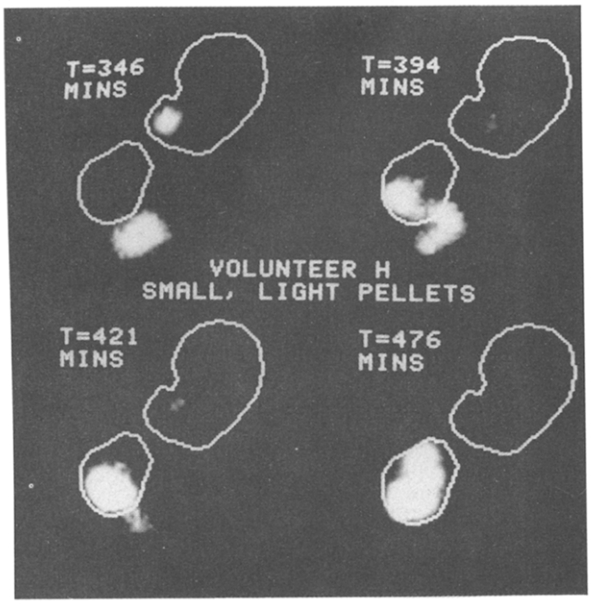


Fig. 5. Gastric emptying of small, light pellets.

Fig. 6. Gastric emptying of small, heavy pellets.

ing times for the small pellets revealed a significant difference between the pellet densities. The 50% emptying time was delayed by an average of 16 min, from 125 min for light pellets to 141 min



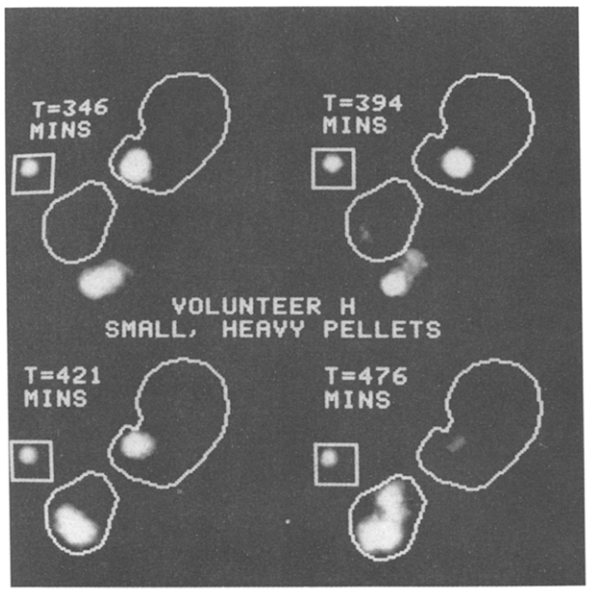
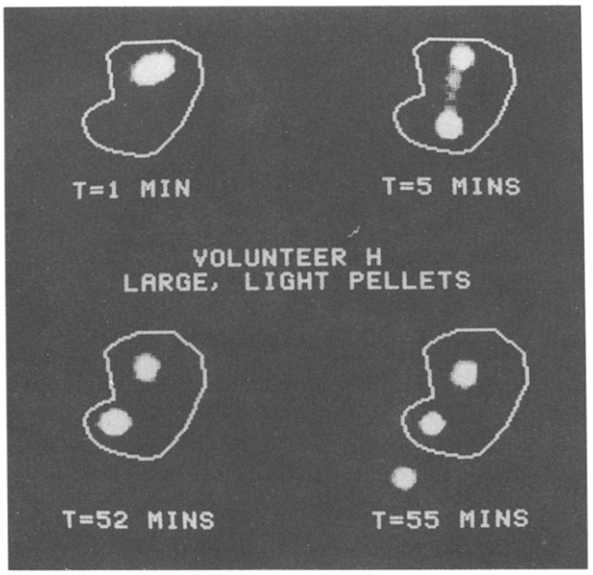


Fig. 7. Caecal arrival of small, light pellets.

Fig. 8. Caecal arrival of small, heavy pellets.



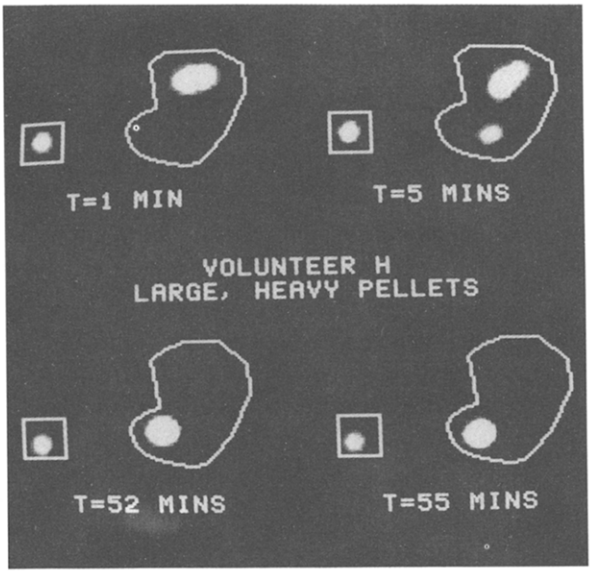
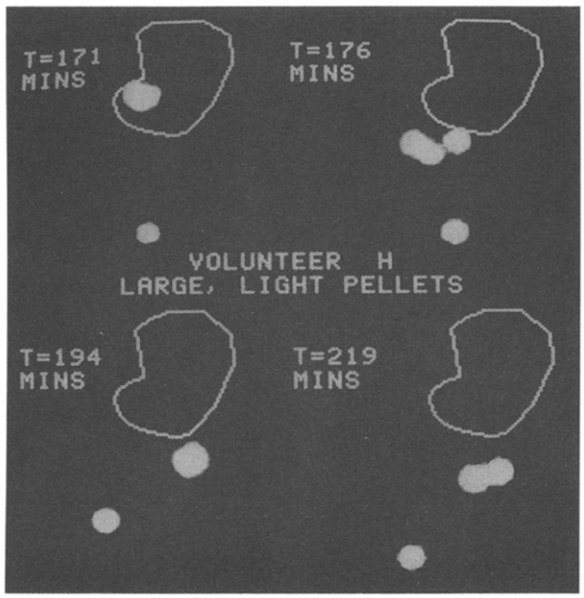


Fig. 9. Commencement of gastric emptying of large, light pellets.

Fig. 10. Commencement of gastric emptying of large, heavy pellets.

for the heavy pellets (Table 1). No such statistically significant difference was observed when the large pellet data were analysed despite the heavy pellet data showing a delay in 50% emptying time



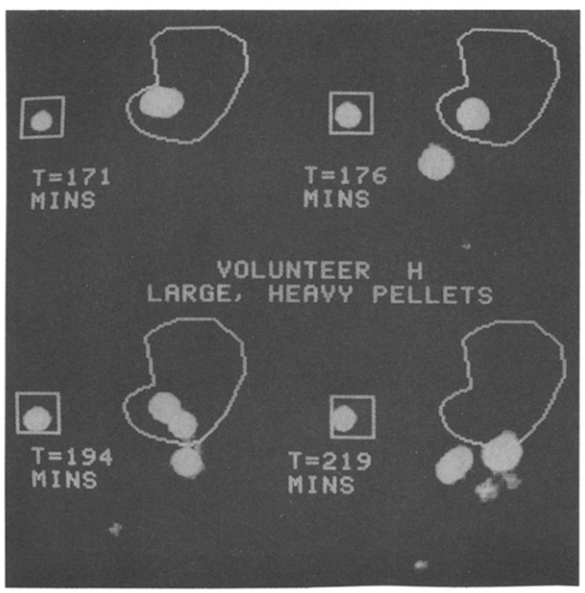
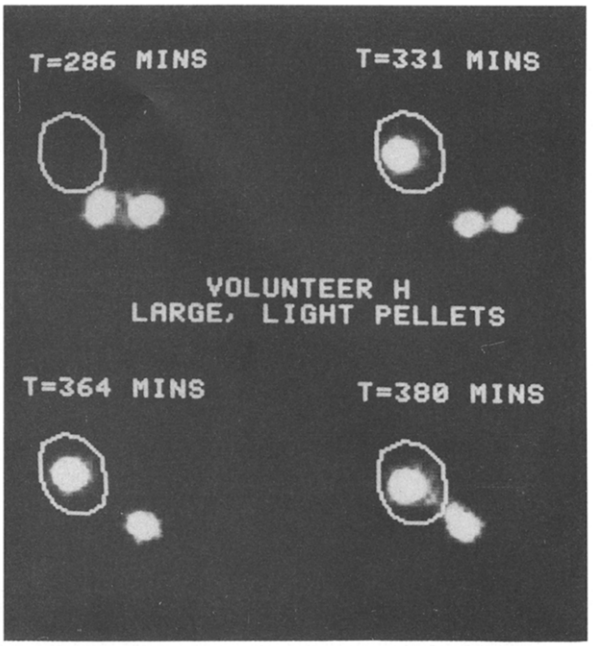


Fig. 11. Gastric emptying of large, light pellets.

Fig. 12. Gastric emptying of large, heavy pellets.

of 21 min, from 107 to 128 min (Table 1). When the data were pooled, no significant differences in the 50% emptying times were found between pellet size or density (Table 4).



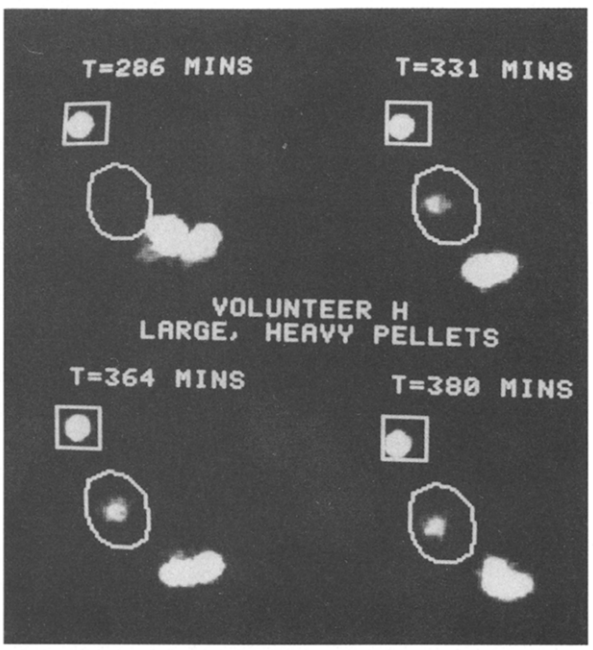


Fig. 13. Caecal arrival of large, light pellets.

Fig. 14. Caecal arrival of large, heavy pellets.

TABLE 1

Individual gastric emptying values

Subject	G50 (min)				AUC			
	Small		Large		Small		Large	
	Light	Heavy	Light	Heavy	Light	Heavy	Light	Heavy
A	167	171	161	174	15 300	16 200	17 200	18 200
B	95	97	73	73	8 900	10 100	7 200	7 400
C	72	87	76	77	7 000	8 600	7 200	8 100
D	171	184	98	224	17 600	17 500	10 000	19 500
E	156	188	77	82	15 800	19 100	6 800	9 800
F	48	62	107	103	5 700	7 500	12 200	11 400
G	101	105	89	112	10 200	12 800	7 500	13 100
H	192	237	172	176	20 500	30 000	13 200	19 600
Mean	125	141	107	128	12 600	15 200	10 200	13 400
t-test	$p < 0.05$		n.s.		$p < 0.05$		$p < 0.05$	

TABLE 2

Individual small intestinal residence and caecal arrival times

Subject	SIRT (min)				C50 (min)			
	Small		Large		Small		Large	
	Light	Heavy	Light	Heavy	Light	Heavy	Light	Heavy
A	149	164	153	163	316	335	314	337
B	139	168	247	267	234	265	320	340
C	281	307	241	388	353	392	317	465
D	74	69	113	60	245	253	211	284
E	164	188	207	291	320	376	284	373
F	167	171	228	234	215	233	335	337
G	133	181	170	168	234	286	259	280
H	208	236	159	355	400	473	331	531
Mean	164	186	190	241	290	327	296	368
t-test	$p < 0.01$		n.s.		$p < 0.01$		$p < 0.05$	

TABLE 3

Mean gastointestinal transit parameters, pooled by (a) density and (b) size

	G50 (min)	AUC	SIRT (min)	C50 (min)
(a) Pooled data by density				
Light pellets	116	11 400	177	293
Heavy pellets	135	14 300	213	348
(b) Pooled data by size				
Small pellets	133	13 900	175	308
Large pellets	117	11 800	215	332

TABLE 4

Summary analysis of variance table

Source of variation	df	*F*			
		G50	AUC	SIRT	C50
Between subjects	7	9.61 [b]	7.38 [b]	10.48 [b]	9.70 [b]
Between pellet size	1	2.34	3.14	7.88 [a]	2.87
Between pellet density	1	3.08	5.78 [c]	6.31 [a]	14.50 [b]
Interaction	1	0.05	0.07	1.08	1.49
Residual	21				

[a] Significant at 5% level.
[b] Significant at 1% level.

Paired *t*-tests performed on normalised values for AUC showed that with both pellet sizes an increase in pellet density resulted in a significant increase in the value for AUC (Table 1). Pooling the data revealed that the AUC was still significantly greater for the heavier pellets (Table 4). No significant differences were found between values for AUC for different pellet sizes (Table 4).

Paired *t*-tests performed on values for SIRT revealed a highly significant ($p < 0.01$) increase in SIRT of 22 min for small heavy pellets (186 min) compared with the mean value for small light pellets (164 min). There was no significant difference in SIRT for large pellets (Table 2). Analysis of variance on the pooled data revealed that SIRT of heavy pellets and large pellets was significantly prolonged (Table 4).

The time from ingestion for 50% of the pellets to enter the caecum was significantly prolonged by the heavy pellets for each pellet size when analysed separately (Table 2). For small pellets, the mean prolongation was 37 min, from 290 to 327 min ($p < 0.01$). For large pellets the mean delay in time for 50% of pellets to enter the caecum was 72 min ($p < 0.05$). Pooling the data showed no significant difference in caecal arrival by pellet size, but a highly significant ($p < 0.01$) delay in caecal arrival with pellet density. The overall mean delay in caecal arrival was 55 min with heavy pellets (348 min) compared to light pellets (293 min).

Discussion

Gastric emptying of pellets was found to be prolonged by an increase in the density of the pellets, but was not affected by the size of the pellets. There was no evidence that the small pellets emptied from the stomach with the co-administered liquid. The emptying of the small pellets was typically preceded by a lag period, unlike the emptying behaviour of liquids. It would appear that size alone is not the only factor that determines whether stomach contents empty as a liquid.

Extended gastric residence of pellets of higher density was reflected in the values for normalised AUC. Analysis of variance on the pooled times for 50% gastric emptying data did not reveal a significant difference in emptying between the different densities of pellets. When the results to the paired *t*-tests were considered, this non-significance was found to be a consequence of the large pellet data. Gastric emptying of the small pellets was significantly prolonged with the increase in density.

It appeared that the variability of the emptying of the large pellets precluded the detection of any real differences between the formulations. Chance emptying of one or two of the small pellets had a negligible effect on the overall transit pattern of this formulation whereas this was not true for similar chance emptying of the larger units, of which there were only four per dosage form. This chance emptying or 'fortuitous emptying' is not uncommon, and was described by Dozois et al. (1971), who observed the process in fasted dogs. They suggested that large objects might occasionally become 'trapped' in the terminal antrum and might empty as the pylorus opens, because of the pressure differential between stomach and duodenum. This demonstrates one advantage of a multiple unit formulation.

The prolongation of gastric emptying with units of increased density confirms the findings reported by Devereux (1987). An earlier study by the authors (Clarke et al., 1993) indicated that there was no significant prolongation of gastric emptying at densities up to 2.4 g cm^{-3}, suggesting that the critical density lies between 2.4 and 2.8 g cm^{-3}. The current study indicates that there may be a threshold density, of the order of 2.4–2.6 g cm^{-3}, above which gastric emptying is prolonged. It may be that further increases of the density of the pellets, greater than have been studied by Clarke et al. (1993) and Devereux (1987), might result in an even more effective prolongation of gastric emptying.

A proposed explanation for the difference in rate of gastric emptying may be that the greater density of the heavy pellets provides them with an increased resistance to the normal contractions of the stomach. Since this feature is not afforded to the light pellets, these pellets tended to empty in

advance of the heavy pellets. The heavy pellets may also be able to settle deeper into the folds of the stomach, this offering even more protection against normal gastric emptying.

Pellets within the stomach showed little dispersion, although they did occasionally disperse during transit along the small intestine. However, in most cases arrival of the pellets at the ileocaecal junction was characterised by their collection and stagnation in the region of the lower right ileac fossa. Such periods of stasis at the ileocaecal junction have been observed for other pharmaceutical dosage forms (Davis et al. 1984, 1988; Hardy et al. 1986; Wilson et al. 1986). After a period of little movement there was bolus entry of most, or all, of the pellets into the caecum. Caecum arrival could often be correlated with meal ingestion, either lunch at 210 min or a cup of tea at 390 min. This phenomenon was first recognised radiographically by Hertz in 1913. He observed that bismuth containing chyme reached the end of the ileum 1 h or even longer before any appreciable quantity passed into the caecum. During this time there were very few peristaltic contractions. In contrast, the ingestion of food never failed to promote peristalsis in the region of the sphincter. This event has been termed the gastro-ileal reflex and has been observed more recently by Kerlin and Phillips (1982) and Hardy and Perkins (1985).

In this study, small intestinal residence time was found to be significantly prolonged by the increase in pellet density and the increase in pellet size. This has not been observed previously.

Although differential small intestinal transit of dosage forms has not been demonstrated before, Najib et al. (1985) had proposed the theory that flow in a horizontal tube might be similar to passage of particles along the intestine. According to this theory, the rate of intestinal transit would be dependent on factors such as intestinal mobility, particle diameter, particle shape, particle density and the viscosity of the suspending fluid. An increase in particle diameter or density of the particles was observed as an increase in critical velocity. Although the model proposed by Najib et al. (1985) is a very simplified representation of the gastrointestinal tract, the results observed in this study fit the theory. Small intestinal residence time was significantly prolonged by the increase in density, presumably because flow of the heavier units did not occur until a higher critical velocity. Similarly, the larger units traversed the small intestine more slowly than the smaller units as they also require a higher critical velocity in order to flow.

The significant prolongation of small intestinal transit shown by large and heavy pellets is one of the few reports in which a normal differential SIRT has been demonstrated. Devereux (1987) studied units of comparable density to those used in this study, but although she noted a prolongation of SIRT of 26 min with the heavier units in fasted subjects, this was not statistically significant.

The arrival of the dosage form in the caecum is reflected by the average gastric emptying time and the small intestinal residence time. Therefore, the heavy pellets, which demonstrated both a significantly extended gastric residence period and a significantly prolonged SIRT showed a highly significant delay in arrival at the caecum. Oro-caecal transit time was delayed by approx. 20%, from 5 to 6 h by the heavier pellets. Although large pellets took significantly longer to travel the length of the small intestine, their arrival at the caecum was not delayed compared to small pellets.

Conclusion

The transit of heavy pellets, through the gastrointestinal tract to the caecum, appeared to be delayed at all levels. The effects of extended gastric residence and prolonged small intestinal residence time are additive, resulting in a greater delay in arrival at the caecum, and consequently prolonged residence in the upper parts of the intestine where absorption is preferred. For a drug that is not absorbed extensively from the colon, the longer the dosage form remains in the proximal regions of the gut, the more drug will be absorbed over an extended period of time, thereby improving the bioavailability of a sustained release formulation and enabling prolongation of

the dosage interval. For most drugs, both extended gastric residence and prolonged small intestinal transit will improve the efficacy of the dosage form. However, if the drug is required to act locally in the stomach, or is absorbed at a 'window' in the proximal small intestine, retention of the dosage form in the stomach would be the preferred option.

The size of the pellets seemed to have little effect on gastrointestinal transit. Small intestinal transit was significantly prolonged by the larger pellets, but this did not significantly prolong the more important parameter of caecum arrival time.

Of the four formulations, small heavy pellets are recommended as the optimum dosage form, the smaller pellets chosen in preference to the large pellets as they have been shown in these studies to perform more reliably and reproducibly in vivo.

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