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Gastrointestinal transit of pellet systems in ileostomy subjects and the effect of density

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The transit of pellets of different densities (0·94 and 1·96 g cm^{-3}) through the gastrointestinal tract of ileostomy subjects has been followed using the technique of gamma scintigraphy. In contrast with earlier reported results, the transit of the pellets was not affected by particle density.

The biological availability of a drug from an oral dosage form can be affected by a variety of physiological factors that include gastric emptying time and intestinal motility. Gastric emptying is controlled by neural and hormonal regulation and is influenced by factors such as the composition and volume of stomach contents, acidity and osmolarity (Minami & McCallum 1984). Fluids and small particles are emptied from the stomach more rapidly than solids which are held back at least to some extent at the pylorus until they have been reduced in size to allow passage through the pyloric sphincter. The liquid phases of meals empty from the stomach with half-times from about 30–180 min, while the solid phases empty more slowly, with half-times ranging from ca 60–240 min (Christian et al 1980). Not only are the half-times different but so also are the kinetics, the emptying of liquids being described by an exponential function and the emptying of solids by an approximate zero-order function (Minami & McCallum 1984).

Multiple unit dosage forms consisting of small pellets of about 1 mm diameter are able to pass through the pyloric sphincter during normal gastric emptying. Consequently, pellets are emptied gradually from the stomach. The gastrointestinal transit time of pellets has been only sparsely investigated due to the lack of reliable methods of investigation. Studies have thus been performed in subjects having an ileostomy (Hinton et al 1969; Bechgaard & Ladefoged 1978) as well as in subjects with intact gastrointestinal tracts (Bogentoft et al 1982; Davis et al 1984). The average transit times through the stomach and small intestine of low density multiple unit dosage forms were typically in a range from 4 to 8 h (Bechgaard & Christensen 1982; Davis et al 1984).

Various attempts have been made to control the gastrointestinal transit of dosage forms by exploiting physiological and formulation factors. Thus Bechgaard & Ladefoged (1978) investigated the effect of pellet density on gastrointestinal transit time in ileostomy subjects. The average transit times for light and heavy pellets were 7 and 25 h, respectively. The diameter of the pellets was of minor significance. However, in more recent studies using external scanning, Bogentoft et al (1982) were unable to confirm in healthy subjects an extended gastrointestinal transit time that could be attributed to density. Additionally, Kaus et al (1984) showed that transit through the small intestine was independent of particle density in normal subjects.

To investigate further the effect of particle density on gastrointestinal transit in ileostomy subjects a study has been undertaken in seven subjects using pellet formulations of densities 0·94 and 1·96 g cm^{-3}. The transit of the pellets from mouth to ileostomy bag has been followed by labelling the pellets with two different gamma emitting radionuclides and visualizing the material in different regions of the gastrointestinal tract by means of a gamma camera.

MATERIALS AND METHODS

Materials

Non-toxic light pellets of density 0·94 g cm^{-3} (sieve fraction 0·7–1·0 mm) were prepared from hard paraffin and labelled with technetium-99m using ^{99m}Tc-sodium pertechnetate obtained by elution from a generator. Non-toxic heavy pellets of density 1·96 g cm^{-3} (sieve fraction 0·7–1·0 mm) were prepared using barium sulphate and were labelled with indium-111 using ^{111}In-indium chloride solution in

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0·04 M hydrochloric acid (Amersham International, Aylesbury, UK).

Subjects and methods

Seven ileostomy subjects, 5 male, 2 female, aged 29–62 years, participated with their informed consent in the assessment which had received approval from Nottingham University Ethical Committee. Total or part proctocolectomy had been performed as a consequence of ulcerative colitis or carcinoma of the colon. The small intestine was intact in all subjects. Typically the terminal ileum was the site of the ileostomy. During the three months before the study the subjects appeared normal. The time elapsed from ileostomy ranged from one to 28 years. One individual was prescribed 60 mg codeine phosphate daily to counteract loose motions.

On the day of the study, each subject was allowed a light breakfast and was administered the labelled light (technetium-99m) and heavy (indium-111) pellets (approximately 500 in number) suspended in a mixture of 100 g Complan in 300 ml water. Subsequently the subjects were allowed to drink and eat normally during the course of the study. The administered radioactivity for each formulation was approximately 4 MBq. Simultaneous imaging of both radionuclides was undertaken with a gamma camera having a field of view of 40 cm diameter, fitted with a medium energy (300 keV maximum energy) parallel hole collimator and with the subjects standing. External anatomic reference markers made from adhesive tape labelled with a small quantity of ^{99m}Tc-sodium pertechnetate were positioned anteriorly and posteriorly over the liver to the right of the stomach. Anterior and posterior images of 60 s duration were taken at suitable intervals over 10 h, with additional imaging at 24 h where possible. The data were recorded on a computer for analysis later. The images were displayed on a television monitor and regions of interest were defined around the stomach and ileostomy bag. The count rates recorded in these regions were quantified and corrections were made for background activity. Correction was made for the 'scatter down' of the higher energy radiation (from indium-111) into the energy window of the lower energy photopeak (of technetium-99m). A correction factor was obtained by administering the indium-labelled pellets before the technetium-labelled pellets and imaging on both energy channels with indium-111 alone. The corrected technetium count rates and the indium count rates were then further corrected for radioactive decay. A geometric mean of the anterior and posterior counts was then taken to give a result for activity that was approximately independent of the depth of the source (Hardy & Perkins 1985). This technique has become well established for clinical studies of gastric emptying. Christian et al (1980) verified the accuracy of the procedure by in-vitro and in-vivo studies, and used indium-111 and technetium-99m to radiolabel, respectively, the liquid and solid phases of a meal.

Filled ileostomy bags were also imaged on the second day of the study.

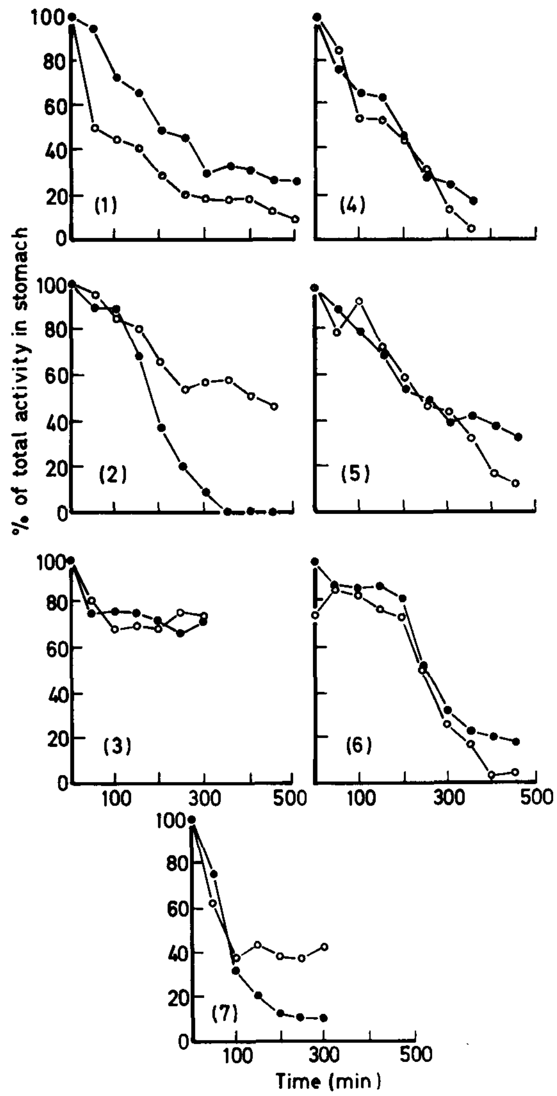

FIG. 1. Composite figure showing individual gastric emptying activity–time profiles for the 7 ileostomy subjects (○ heavy, ● light pellets).

RESULTS AND DISCUSSION

The individual profiles for gastric emptying of the pellets are shown in Fig. 1. There are intersubject differences in gastric emptying behaviour, but for a given individual the patterns for both heavy and light pellets are generally similar. Some individuals (e.g. subject 7) demonstrated relatively rapid emptying of both types of pellet (t50% approximately 80 min), whereas for others (in particular subject 3) the gastric emptying was slow. The differences between the gastric emptying of light and heavy pellets (expressed as a percentage) at selected times were calculated for each subject and the mean differences obtained for a pooled sample are shown in Fig. 2, together with the standard error. The mean differences between light and heavy pellets were in all cases less than 10%.

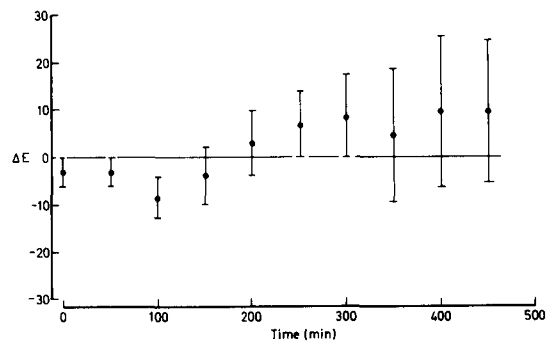

FIG. 2. Differences in the gastric emptying of pellets expressed as ΔE = % emptied heavy −% emptied light.

The pooled transit data are given in Fig. 3 and show a linear relation between gastric emptying and time. There is no statistical difference between the light and the heavy pellets with respect to gastric emptying time using parametric (Student's paired *t*-test on selected times and for all times) and non-parametric (Mann-Witney test) methods. The mean times for 50% emptying are 200 and 225 min for the light and heavy pellets, respectively.

The transit of activity to the ileostomy bag was slow and in some cases it was not possible to collect data over a sufficiently extended period of time. The available data have been tabulated at selected time intervals to show the percentages of light and heavy pellets (Table 1). The available data have been pooled to provide the two curves in Fig. 3. Once again no statistical difference could be found between light and heavy pellets. The corresponding data from the work of Bechgaard & Ladefoged (1978) are included in Fig. 3 for comparative purposes.

The lack of differences in gastrointestinal transit for low and high density pellets are in accordance with results obtained in healthy subjects (Bogentoft et al 1982; Kaus et al 1984) but contradict results obtained earlier for ileostomy subjects (Bechgaard & Ladefoged 1978). The major differences in design

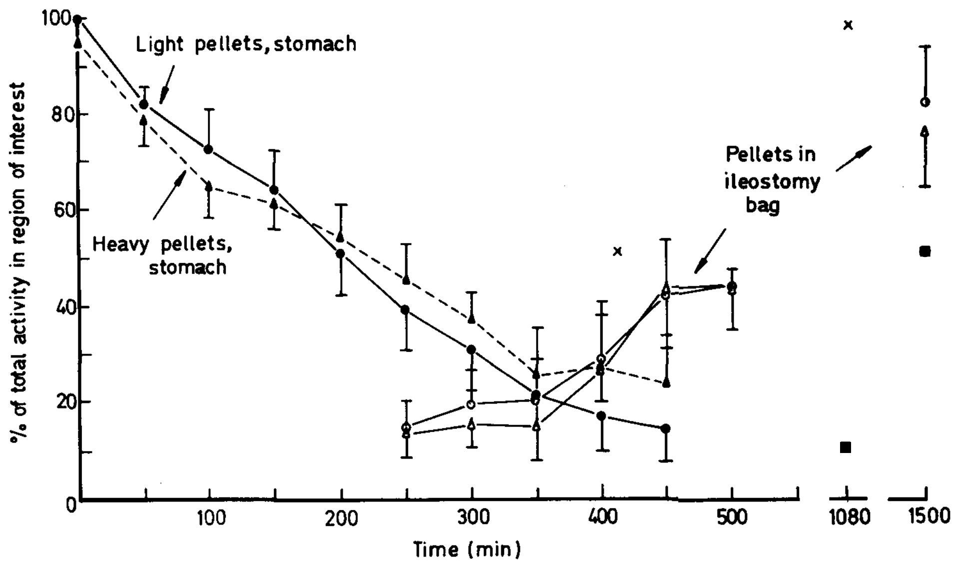

FIG. 3. The gastrointestinal transit of heavy and light pellets in ileostomy subjects (mean ± s.e.m., n = 7) (gastric emptying, ● light and ▲ hevy pellets; ileostomy bag filling, ○ light and △ heavy pellets; data from Bechgaard & Ladefoged (1978), ■ heavy and × light pellets).

Table 1. Intestinal transit of pellets. Percentage of initial dose in ileostomy bags at selected times (min).

	Light pellets (Tc-99m)			Heavy pellets (In-111)		
Subject	300	500	1500[a]	300	500	1500[a]
1	11	33	62	25	43	64
2	14	38	100[c]	8	24	100[c]
3	9	—	90[b]	4	—	75[b]
4	35	63	—	19	49	—
5	0	0	—	9	12	—
6	—	45	—	—	34	—
7	15	—	—	4	—	—
Mean	14	36		11·5	32	
s.e.m.	4·7	10		3·5	6·6	

[a] Approximate time (values in the range 1200–1600 min).
[b] Value obtained by mass balance from remaining whole body activity.
[c] Estimated from total lack of activity in body.

between the study by Bechgaard & Ladefoged (1978) and the other studies were the method of registration of the number of pellets, fasting conditions and the use of ileostomy subjects. During both the present study, and that of Bechgaard & Ladefoged (1978), the subjects were in upright postures and moderately active. Bechgaard & Ladefoged (1978) registered the arrival of particles in ileostomy bags visually, whereas in more recent studies gamma scintigraphy has been used. Unfortunately, the pellet recovery procedure did not include in-vivo imaging, and therefore no information was obtained on the relative rates of transit through different regions of the gastrointestinal tract. Fasting or fed conditions, although having some influence on gastrointestinal transit (Bogentoft et al 1982) would not be expected to give rise to the considerable difference for heavy pellets observed by Bechgaard & Ladefoged (1978). Interestingly in the subject with a high beer consumption during Bechgaard & Ladefoged's study, the transit times were the same for both the heavy and light pellets. Thus the type of food consumed during the study may have had a bearing on the results.

CONCLUSIONS

With the method of gamma scintigraphy, no difference between the gastrointestinal transit of light and heavy pellets has been found, up to at least 8 h after administration. At longer times a definite conclusion cannot be made because of methodological limitations.

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