*International Journal of Pharmaceutics*, 21 (1984) 167–177
Elsevier



IJP 00717

# A comparative study of the gastrointestinal transit of a pellet and tablet formulation

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(Received March 14th, 1984)
(Accepted May 2nd, 1984)

## Summary

The gastrointestinal transit of a pellet and tablet formulation have been evaluated in a group of 6 subjects using the technique of gamma-scintigraphy. Each formulation was labelled with a different radionuclide and the preparations administered concurrently. The transits of the formulations were found to be highly dependent on food intake and there was a good correlation between transit times (gastric emptying, arrival at colon) and the calorific value of the meal taken shortly before dosing. In some cases the pellet system emptied rapidly from the stomach and showed little spreading in the small intestines.

## Introduction

Controlled release dosage forms such as pellet systems and matrix tablets are becoming popular in drug therapy as attempts are being made to extend the biological half-life of certain drugs. The transit of the dosage form through the gastrointestinal tract can have an influence on the appearance of the drug in the systemic circulation (bioavailability). The time the dosage form remains in the

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stomach is of particular significance and it is now well established that the stomach handles solid objects greater than 2 mm in diameter in a different manner to smaller objects or liquids. In addition, factors such as emotional state and diet are important determinants of gastric emptying (Kelly, 1981). It is sometimes claimed that a pellet system is more appropriate for the controlled release of drugs since the individual particles will be widely dispersed in the gastrointestinal tract. The advent of gamma-scintigraphic methods now allows such speculation to be examined in a quantitative way and various studies (Casey et al., 1976; Daly et al., 1982; Davis, 1983) have demonstrated clearly the considerable advantages that scintigraphy has over radiographic procedures for following gastrointestinal transit.

A number of recent investigations (Hunter et al., 1982; Christensen et al., 1984) have shown that pellets can sometimes move as a bolus through the intestines and that such behaviour is highly dependent on the presence of food in the stomach.

The present study was undertaken to follow the transit of a pellet system and a non-disintegrating tablet, through the gastrointestinal tract of healthy volunteers following a light breakfast. The two systems were labelled with different radionuclides so that both could be monitored concurrently.

## Materials and Methods

*Labelled pellets*

An ion exchange resin (Amberlite IRA 410, density 1.2 g/cm$^3$) was sieved to provide particles in the size range 0.8–1.1 mm diameter and labelled by mixing 1 g with 50 MBq technetium-99m using $^{99m}$Tc-sodium pertechnetate obtained from a generator (Amersham International). Size 3 hard gelatin capsules were each filled with approximately 200 particles (140 mg) to give an activity of about 2 MBq of $^{99m}$Tc at the time of administration.

The stability of the binding of the label to the ion exchange resin was checked in vitro under pH and ionic strength conditions relevant to the gastrointestinal tract (Casey et al., 1976; Curt et al., 1980; Hunter et al., 1982). A further check was made in vivo by monitoring the thyroid glands of the volunteers, since released pertechnetate would concentrate at this site. Christensen (1984) has described in detail the in vitro evaluation of coated pellet systems and tests for the integrity of the labelled preparations. The ion exchange pellets used in the present work had the same gastrointestinal transit behaviour (gastric emptying and intestinal transit) as labelled coated pellets (Christensen, 1984) for the same volunteer and for different volunteer groups (Davis, 1983; Christensen et al., 1984).

*Labelled tablets*

Concave oblates with a diameter of 8 mm and thickness 4.5 mm were prepared from lactose in a manner similar to that described by Daly et al. (1982). Prior to compression the lactose was mixed with a small quantity (20 mg) of a diethylenetriaminepentaacetic acid) (C.I.S. (U.K.), London) radiolabelled with 4 MBq indium-111 per tablet.

The tablets were coated with polymethylmethacrylate to prevent their disintegration. The integrity of the tablets was checked in vitro under simulated conditions relevant to the gastrointestinal tract.

The average weight of the tablets was 300 mg and the density 1.39 g/cm$^3$ (as measured by mercury pycnometry).

*In vivo studies*

A group of 6 healthy male volunteers aged 19–30, height 1.62–1.88 m, weight 60–85 kg, participated with informed consent. Each was allowed to have, if desired, a breakfast (for example, cereal, coffee or tea, egg, toast, butter, marmalade) at least one hour before the commencement of the study. Each volunteer swallowed the pellets and tablet with 100 ml of water.

Simultaneous imaging was undertaken of both radionuclides with the subjects standing, using a gamma camera having a 40 cm diameter field of view and fitted with a medium energy (300 keV maximum energy) parallel hole collimator. An external reference marker comprising an adhesive patch labelled with a small quantity of $^{99m}$Tc-sodium pertechnetate was positioned over the liver to the right of the stomach. Anterior and posterior images each of 60 s duration were taken at intervals over a period of 24 h and the data recorded by computer for analysis. Subsequently regions of interest were defined around the images of the stomach and ascending and transverse colon, and the activity in these regions quantified and corrected for background activity. When undertaking imaging using two radionuclides, correction needs to be made for 'scatter down' of the activity of the higher energy radiation from indium-111 into the energy window of the technetium-99m photopeak. A correction factor was obtained by administering the indium labelled tablet and imaging on both channels with indium-111 alone immediately before giving the technetium-labelled preparation. The counts were then corrected for radioactive decay. The attenuation of the radiation by overlying tissues can give rise to incorrect estimates of the amounts of radioactivity in vivo when unidirectional images are taken (Tothill et al., 1978). The use of the geometric mean of the anterior and posterior counts gives a result that is approximately independent of the depth of the source. This procedure was adopted in the present study. The volunteers were allowed to drink and eat normally during the study.

## Results and Discussion

The transit of the pellets and tablet system through the gastrointestinal tracts of the volunteer group was followed using the gamma camera method. A typical set of radionuclide images for one volunteer is shown in Fig. 1. The indium and technetium images recorded simultaneously have been combined to show the pellet system and the tablet in the same view. The tablet and the pellets in the stomach and the transit through the intestines can be seen. In two views the tablet is seen to be contained within the pellet mass. The pellets spread to some extent but do not distribute particularly widely within the intestines. At longer times the tablet is

further advanced in the colon than the pellets. The data have been quantified to allow the calculation of profiles for gastric emptying and arrival at the ileo-caecal junction (Table 1 and Fig. 2).

The transit of the pellets in these two different regions of interest is expressed as the time for 50% to leave or arrive at the particular site. It will be noted that for some volunteers the emptying of the pellets as well as the tablet formulation from the stomach was rapid whereas for other volunteers a slower emptying was observed (Fig. 3). A value for spreading can be estimated from the reciprocal of the gradient of the gastric emptying or colonic arrival curve (if necessary drawn as a tangent to the curve at 50% activity) expressed as minutes.

The data for the pellet system are in good agreement with previous investigations that have employed gamma-scintigraphy to follow gastrointestinal transit (Hunter et al., 1982; Sjögren and Bogentoft, 1982; Christensen et al., 1984). The recorded times for 50% to leave the stomach were between 80 and 180 min for either fasted volunteers or following a light breakfast.

Data for the emptying behaviour of the individual tablets and their arrival in the colon are also given in Table 1 (as approximate times since the imaging was not

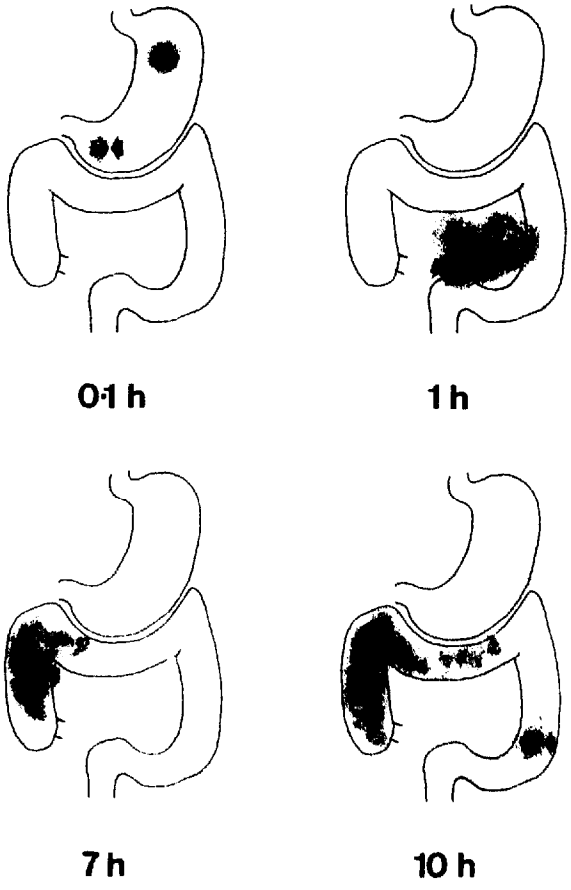


Fig. 1. Radioisotope images showing the pellet and tablet formulations in different regions of the gastrointestinal tract. The position of the tablet has been identified by an arrow.

TABLE 1

GASTROINTESTINAL TRANSIT OF PELLETS AND TABLET FORMULATIONS

| Volunteer | Pellets ($t_{50\%}$) (min) | | | Tablet (min) (approx. times) | | |
|---|---|---|---|---|---|---|
| | Gastric emptying | Colonic arrival | Transit through small intestines | Gastric emptying | Colonic arrival | Transit through small intestines |
| 1 | 125 | (600) [b] | (475) [b] | 600 | ( > 660 < 1400) [b] | – |
| 2 | 30 | 180 | 150 | 30 | 216 | 186 |
| 3 | 150 | 700 | 550 | 225 | 500 | 275 |
| 4 | 33 | 275 | 200 | 42 | 219 | 177 |
| 5 | 75 | 200 | 125 | 30 | 180 | 150 |
| 6 | 60 | 170 | 110 | 60 | 213 | 153 |
| Mean | 79 (50) [a] | 305 (275) [a] | 227 (225) [a] | 164 | 265 | 188 |
| S.E.M. | 20 | 100 | 82 | 92 | 59 | 23 |
| n | 6 | 5 | 5 | 6 | 5 | 5 |
| Median (between) | | | | 42 and 60 min | 216 and 219 min | 177 and 186 min |

[a] Number in parentheses from Fig. 1 — pooled data.

[b] Data excluded from calculations since transit to colon for tablet greater than 660 min.

continuous) and in Fig. 2 as the number of units in a given region at any given time. In this case emptying is an 'all-or-nothing' process that cannot be compared directly with the statistical process for the emptying of a multiple pellet system. However, it is apparent that the individuals who exhibited slow emptying of pellets also gave a delayed emptying for the tablet. This interrelationship is shown in Fig. 4 for both gastric emptying and colonic arrival. If data for volunteer 1 are omitted (since no time for arrival at the ileocaecal junction was obtained) then the relationship

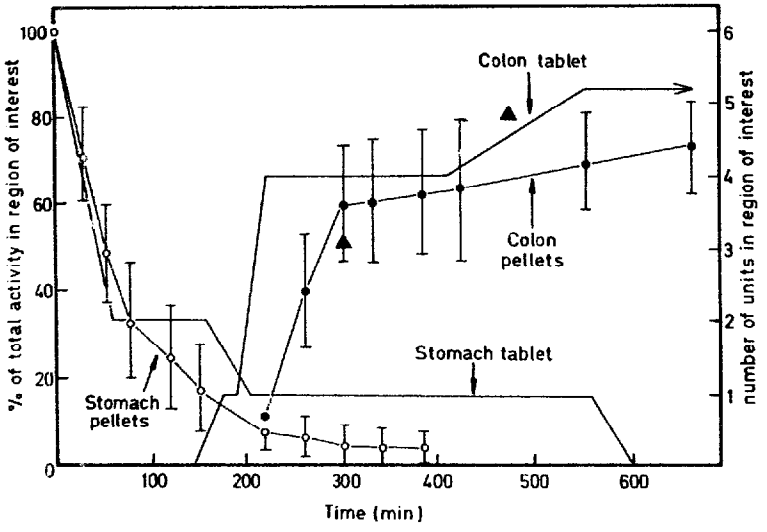


Fig. 2. Gastrointestinal transit of pellet and tablet systems. ▲, data from the study of Dew et al. (1982). Pellet data mean ± S.E.M. (n = 6).

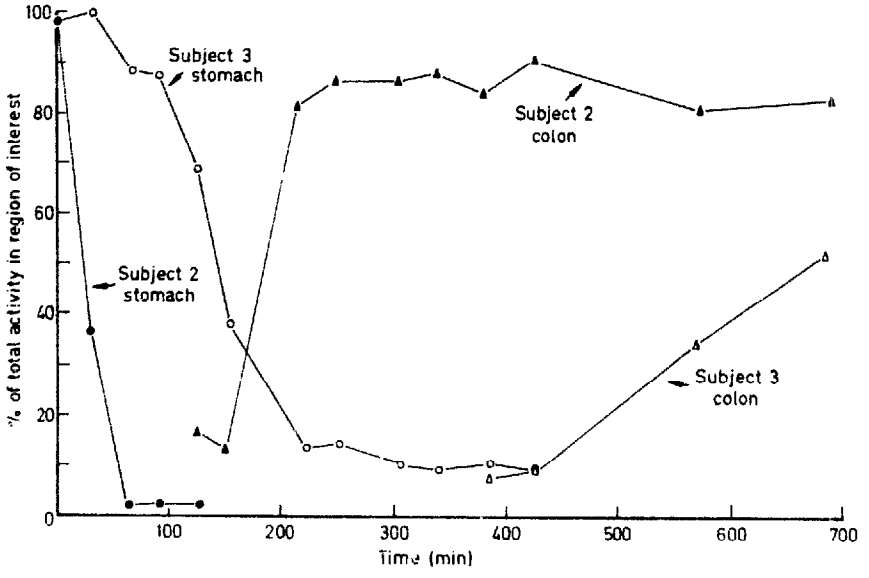


Fig. 3. Gastrointestinal transit of pellets in two different volunteers.

between the data can be expressed as:

$$t_{pellet,50\%} = 1.3\ t_{tablet} - 35.8$$

correlation coefficient = 0.95, n = 10, $P < 0.001$.

The gastric emptying of single unit dosage forms of similar diameter to those in the present study has been examined by various authors (Sjögren and Bogentoft, 1982; Rosswick et al., 1967; Muller-Lissner and Blum, 1981). The range has been from 30 min to more than 24 h. Recent studies performed by external scanning have reported gastric emptying times ranging from 0.5 to 4.5 h (median 2 h) in the fasting state and from 2 to 4.5 h (medium 4 h) after a meal (Sjögren and Bogentoft, 1982). The variation in gastric emptying between individuals in the present investigation is attributed to idiosyncratic effects as well as possible effects due to the different natures of the 'breakfast' taken before the study. This will be discussed further below. The data on the transit of the pellets (50% arrival at caecum) and tablets through the small intestine indicate a mean transit time from mouth to caecum of about 4–6 h and for stomach to caecum of 3–4 h. Christensen et al. (1984) reported mean values of 246 ± 28 min (n = 5) and 204 ± 31 min (n = 8) for the transit through the small intestine of solution and pellet systems, respectively. The values in Table 1 for pellets (227 ± 82 min, n = 5) and tablet (188 ± 23 min, n = 5) are in good agreement and indicate that transit in the small intestine is little affected by the size or shape of the particles. The few data available for the transit of single unit dosage forms from stomach (or mouth) to colon are in accord with the present study (Rosswick et al., 1967; Bechgaard and Christensen, 1982; Wilson et al., 1984).

Dew et al. (1982) have recently studied the transit of tablets following breakfast (type unspecified) using a radiographic method. Each of 6 volunteers received 6

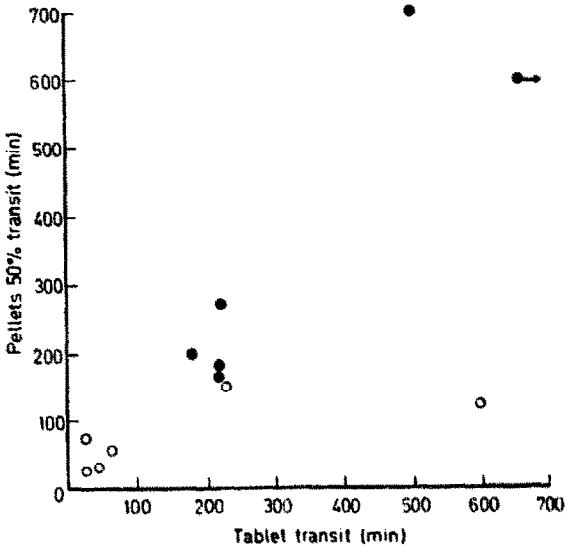


Fig. 4. The interrelationship between pellet data ($t_{50\%}$) and tablet data for gastric emptying (○) and arrival (●) at the colon.

tablets and the recorded data were pooled for purposes of discussion. After 5 h none of the tablets were found in the stomach, 50% were in the small intestine and 50% in the colon. After 8 h, 81% of the tablets had reached the colon (100% by 24 h). The two earlier data points have been included in Fig. 2; the mean value ($t_{50\%}$) of 300 min for mouth-to-colon transit for the tablets agrees well with our data in Table 1.

The data obtained in the present work can be related to the known gastrointestinal physiology. The gastric emptying of pharmaceutical dosage forms will depend upon two major factors; the presence of food in the stomach and the size of the dosage form or for a multiparticulate system the size of the constituent units. The stomach has a remarkable ability to empty different materials in a selective way even though these materials may be ingested simultaneously (Kelly, 1981). Liquids are emptied relatively rapidly but digestible materials need to be broken down into particles of less than 1 mm in size to become suspended in the chyle and then allowed to pass with the liquids through the pylorus into the duodenum (Meyer et al., 1979). This in essence represents a sieving of the solid food. Indigestible solids (such as tablets) of a size greater than about 2 mm are nearly completely retained in the stomach throughout the postprandial period (Hinder and Kelly, 1977). Only when the stomach is empty of digestible matter can the intact tablet be emptied by a special mechanism called the interdigestive myoelectric complex (IMC) (Code and Marlett, 1975).

Powerful contractions have a role in emptying the stomach of its fasting content (swallowed saliva, basal secretion of mucus and cellular debris as well as undissolved tablets). Both liquid and solid gastric content are propelled past the pylorus into the duodenum. The ability of these contractive waves of the IMC to clear the stomach of its contents has been called the 'interdigestive housekeeper' of the gastrointestinal tract (Szurszewski, 1969). Consequently an oral formulation administered to a fasted stomach (or one that has received a light breakfast of low calorific value) may be emptied rapidly from the stomach. Evidence for this has been presented by Hunter et al. (1982) and Christensen et al. (1984) for intact capsules and pellet systems.

After food the stomach has a different emptying pattern that depends on the quantity and quality of food ingested. Carbohydrates empty more quickly than fats but when the total energy is considered isocaloric amounts of fat, protein and carbohydrate empty at similar rates. Thus when meals of different energy content are ingested, the rate of gastric emptying is such that the number of calories delivered to the duodenum tends to be constant with time (Chaddock et al., 1974; Hunt and Stubbs, 1975; Kelly, 1981). In the present study, the good correlation between gastric emptying of pellets and tablets and food intake can be examined by estimating the calorific value of the different breakfasts ingested by the volunteers (Table 2).

The pattern of transit through the intestines is complex and differs between fasted and non-fasted states. Material may lie motionless for some time and then be sequestered into small pieces and pushed to and fro over a short distance within the intestines. As a consequence, the process of transfer is not smooth or uniform (Weisbrodt, 1981). Hard data on the mixing of intestinal contents are lacking but it is believed that there is not appreciable exchange of material at the different levels of

the intestines (Gustavsson, 1978). In fasted individuals it is possible to deliver (radiolabelled) solutions to the ileocaecal junction in an average time of 73 ± 7 min with a range 47 to 140 min (n = 14) (Caride et al., 1982). The IMC again has a role to play and an 'intestinal housekeeper' can move the intestinal contents rapidly down the small intestine into the colon (Szurszewski, 1969). A change in intestinal motility is brought about by eating and hormones released by the presence of different foods have been implicated (Weisbrodt, 1981). The IMC is either disrupted or altered.

Read and others (1982) have failed to show any correlation between gastric emptying and transit time through the small intestine for a large number of normal subjects after they had eaten the same test meal. The rate of gastric emptying influenced the transit of food for the first 70 cm of the small intestine only. The authors suggested that the ileum acted as a buffer region that could delay and concentrate solid material entering from above. Thus passage through the ileum will tend to normalize mouth-to-caecum transit (Read et al., 1982). The observations by Davis (1983), Christensen et al. (1984) that solutions and pellets have similar intestinal transit times, together with the data in Table 1 showing similar transit times for pellets and tablets in the small intestine, provide further evidence for the normalizing role of the small bowel on transit.

The ileocaecal junction forms the boundary between large and small intestines and is a specialized area of the gastrointestinal tract (Weisbrodt, 1981). Most studies indicate that the junction maintains closure between the two regions (Cohen et al., 1968) and prevents retrograde passage of material from the caecum (Christensen, 1981). The movement of material in the colon has been reviewed by Christensen

TABLE 2

FOOD INTAKE BY VOLUNTEERS, ITS CALORIFIC VALUE AND THE RELATION TO GASTRIC EMPTYING

| Volunteer | Breakfast | Calorific value (kJ) | Gastric emptying of pellets | | Emptying of tablets (approx. time) (min) |
|---|---|---|---|---|---|
| | | | $t_{50\%}$ (min) | Spreading value (min) | |
| 1 | 2 sausages baked beans, toast/butter, marmalaoth rade | 3188 | 125 | 330 | 600 |
| 2 | orange juice | 326 | 30 | 50 | 30 |
| 3 | cornflakes, fried egg, toast/butter, tea | 2705 | 150 | 105 | 225 |
| 4 | none | 0 | 33 | 71 | 42 |
| 5 | cornflakes, tea | 1046 | 75 | 128 | 30 |
| 6 | muesli, tea | 1950 | 60 | 100 | 60 |

(1981). The caecum and the sigmoid colon are the major points of delay of material in mouth to anus transit (Hansky and Connell, 1962) and in the present studies we have observed a slow transit of both pellet and tablet formulation in the ascending colon. During the prolonged residence of intestinal contents in the colon mixing can occur. For example, Halls (1965) showed, using different batches of radio-opaque discs of 3 different sizes, that good mixing could occur in the colon even though the discs were ingested 36, 24 and 12 h before the X-ray examination. Furthermore some of the latest ingested discs lay in advance of those ingested earlier. The mixing is believed to occur mainly in the ascending colon (Christensen, 1981).

## Conclusions

The gastrointestinal transit of pellet and tablet formulations in healthy volunteers can be evaluated using the technique of gamma-scintigraphy. Gastric emptying times and intestinal transit times can be related to the calorific value of the breakfast ingested before the study. The average transit times for pellets and tablets in the small intestine are similar and agree well with other data on pellets and solutions (Davis, 1983). The transit behaviour of the formulation can be understood by reference to the known physiological properties of the gastrointestinal tract, in particular the interdigestive myoelectric complex.

## Acknowledgements

The authors wish to thank Dr. M. Wastie, Department of Radiology, Queen's Medical Centre, Nottingham, for advice and helpful discussions.

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