

Alimentary tract and pancreas

Transit of pharmaceutical dosage forms through the small intestine

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SUMMARY The gastrointestinal transit of pharmaceutical dosage forms has been measured in 201 studies in normal subjects using gamma scintigraphy. Solutions, small pellets, and single units (matrix tablets and osmotic pumps) were administered with different amounts of food in the stomach, ranging from fasted state to heavy breakfast. Gastric emptying was affected by the nature of the dosage form and the presence of food in the stomach. Solutions and pellets were emptied even when the stomach was in the digestive mode, while single units were retained for long periods of time, depending on the size of the meal. In contrast, measured intestinal transit times were independent of the dosage form and fed state. The small intestinal transit time of about three hours (mean \pm 1 h SEM) has implications for the design of dosage forms for the sustained release of drugs in specific positions in the gastrointestinal tract.

The main site for the absorption of drugs in man is considered to be the small intestine, with its high effective surface area.¹ Little, if any, drug absorption occurs from the stomach, although some drugs are thought to be absorbed to a limited extent from the large intestine. As a general rule, therefore, drugs should be formulated so that they can be largely absorbed from the small intestine.

Ho, Higuchi, and colleagues^{2,3} have introduced the concept of the 'reserve length' for drug absorption. This is defined as the anatomical length over which absorption of drug can occur, less the length at which absorption is complete. The reserve length is dependent on physiological factors, however, such as bulk flow rate, spreading of the dosage form in the small intestine and the permeability of the drug through the intestinal mucosa.

In the pharmaceutical field, the length of time a dosage form can remain in the small intestine tends to have been overestimated⁴; particularly when consideration is given to controlled release systems designed to provide 24 hour dosage. In some cases insufficient attention has been paid to the influence of gastric emptying, or to the implications of the studies on the nature and function of the migrating myoelectric complex,⁵ and the consequent differ-

ence in the gastrointestinal transit patterns in digestive and interdigestive states. Based on recent physiological studies it could be predicted that a non-disintegrating single unit dosage form would remain in the stomach until the end of the fed phase and then be cleared from the stomach and through to the terminal ileum by the migrating myoelectric complex.⁵⁻⁷ Consequently, small intestinal transit would be expected to be of the order of 1.5-2 hours, provided the interdigestive, or non-fed state was maintained.⁶ Solutions of drugs, or pellet formulations of a size less than about 2 mm would be expected to empty from the stomach during the digestive phase and have similar small intestinal transit times to those reported for meals - about two to four hours.^{6,7}

Various reports have considered the gastric emptying of markers foodstuffs and a variety of dosage forms.⁷⁻¹⁰ Factors such as particle size, calorific values of meals, specific effects of fats, posture, stress etc, have been well described. Detailed studies on the transit from stomach to ileocaecal junction are fewer in number, however.⁶ Read⁷ has commented recently that for the most part gastric emptying and small bowel transit are independent variables, each being controlled by its own regulatory mechanisms.

Several methods are available to measure small intestine transit times.⁶ These include radiography, intubation techniques, metabolisable markers (hyd-

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rogen breath test) and gamma scintigraphy. Each approach has its advantages and disadvantages and in some cases it has been shown that the nature of the test – for example, intubation of the subject, or the use of high osmolarity preparation can alter the normal physiological processes.¹¹ The non-invasive method of gamma scintigraphy now appears to be the method of choice. Recent studies by Caride *et al*,¹² Read *et al*,¹³ 14 Jian *et al*¹⁵ and Malagelada *et al*¹⁶ on foodstuffs and Davis *et al* on dosage forms^{17–20} have shown the usefulness of this technique, particularly when two radionuclides are used simultaneously.

During the last three years we have conducted a number of scintigraphic studies on the gastrointestinal transit of dosage forms, often with a view to relating pharmacokinetic parameters to transit behaviour. Solutions, pellets, and single units (matrix tablets, osmotic pumps etc) have been tested in young adult male subjects and in some cases in elderly women. The dosage forms have been administered with different amounts of food in the stomach; ranging from fasted state to heavy English breakfast. Some of these studies have been published^{17–20} or are in press, while others were conducted as part of work for submission to regulatory authorities. In this paper we have brought together data from 201 investigations in human subjects (representing 23 studies on solutions, 82 on pellets and 96 on single units), in order to consider gastric emptying and transit in the small intestine. The results have implications for the design of pharmaceutical dosage forms, particularly those for controlled or timed release. Additionally, they also have relevance to the design of dosage forms to release drugs at specific positions in the gastrointestinal tract.

Methods

SUBJECTS

Healthy male (aged 29–28 years) and female (aged 29–76 years) volunteers participated in the various studies (Table) after giving informed consent. All protocols were approved by the University of Nottingham ethical committee. The subjects were fasted overnight for at least nine hours before each test. No alcohol was consumed for at least 24 hours before dosing. Smokers and those on any form of medication were excluded.

COMPOSITION OF MEALS

At about 900 am on the day of the study the subjects were given a breakfast, or remained fasting before receiving a selected pharmaceutical formulation. A standard light breakfast (calorific value 1500 kJ)

consisted of buttered toast, marmalade, and orange juice and a standard heavy breakfast (calorific value 3600 kJ) consisted of sausages, bacon, eggs, and bread.¹⁹ On one occasion, subjects were allowed to choose their own breakfast thereby providing a range of different meal sizes.¹⁸

A cup of coffee, or orange juice was provided 1.5–2 hours after dosing, a three course lunch at about three to four hours, a cup of tea, coffee, or orange juice at about seven hours and a dinner at about 10 hours after dosing. The nature of the lunches and dinners varied in the different studies, but in general all volunteers in a given study consumed identical meals. The lunches had an energy content of about 5000 kJ and the dinners 4500 kJ.

MEASUREMENT OF GASTRIC EMPTYING AND INTESTINAL TRANSIT

The various formulations were labelled with gamma emitting radionuclides (technetium 99m, $t_{1/2}=6.0$ h, or indium-111, $t_{1/2}=2.8$ days), so that their transit through the gastrointestinal tract could be followed. Solution formulations contained diethylenetriaminepentaacetic acid (DTPA) labelled with technetium 99m. Pellets were ion-exchange beads (coated and uncoated) of size 0.3–1.2 mm, to which technetium 99m was firmly bound by ion exchange mechanisms.¹⁸ None of these radiopharmaceuticals is absorbed from the gastrointestinal tract. Single unit dosage forms contained either DTPA powder labelled with radionuclide, or entrapped labelled ion-exchange resin. Some single units were formulated to travel the length of the intestines without disintegrating while others were designed to release the labelled material at a rate similar to that of the intended drug, so that *in vivo* release and dissolution profiles could be evaluated and correlated with pharmacokinetic data.²⁰ Details of these formulations can be found elsewhere.^{17–20} Some of the formulations contained active drug, others were placebo. The solid dosage forms were swallowed with 100 ml water. The subjects were imaged using a gamma camera having a 40 cm diameter field of view, fitted with an appropriate parallel hole collimator. Pairs of anterior and posterior images of the abdomen were recorded at suitable intervals with the subjects standing. From the time of dosing and throughout the first day of the study, subjects remained in upright positions (sitting, standing, walking) and undertook a moderate amount of exercise. The images were recorded by computer for analysis. Subsequently the images were displayed on a television monitor and regions of interest were created around the stomach and the colon. The anatomical position of the tracer was

Table Details of pharmaceutical formulations, subjects, and fed states

Study	Formulation	Size (mm)	Subjects	Label	Drug present	Fed state
S1	Solution-DTPA	—	M-5	^{99m} Tc	No	LB
S2	Solution-DTPA	—	M-6	^{99m} Tc	No	LB
S3	Solution-DPTA	—	M-6	^{99m} Tc	Yes	LB
S4	Solution-DPTA	—	M-6	^{99m} Tc	Yes	LB
P1	Pellets	0.3-1.2	M-4	^{99m} Tc	No	FA
P2	Pellets-resin	0.5-1.8	M-6	¹¹¹ In	No	FA
P3	Pellets-resin	0.5-1.8	F-5D	¹¹¹ In	No	FA
P4	Pellets-resin	0.5-1.8	F-5C	¹¹¹ In	No	FA
P5	Pellets	0.8-1.2	M-6	^{99m} Tc	No	VA
P6	Pellets-coated	0.7-1.0	M-8	^{99m} Tc	No	LB
P7	Pellets-coated	0.7-1.0	M-4	^{99m} Tc	No	LB
P8	Pellets	0.7-1.0	M-6	^{99m} Tc	No	LB
P9	Pellets	0.6-0.8	M-8	^{99m} Tc	No	LB
P10	Pellets	0.8-1.2	M-6	^{99m} Tc	Yes	LB
P11	Pellets	0.6-0.8	M-8	^{99m} Tc	No	HB
P12	Pellets	0.8-1.2	M-6	¹¹¹ In	Yes	HB
P13	Pellets-coated	0.7-1.0	M-4	^{99m} In	No	HB
P14	Pellets	0.7-1.0	M-6	^{99m} Tc	No	HB
T1	Tablet, slow release	17×4	M-6	¹¹¹ In	Yes	FA
T2	Capsule, non-disintegr.	25×9	M-6	^{99m} Tc	No	FA
T3	Capsule, non-disintegr.	25×9	F-5D	^{99m} Tc	No	FA
T4	Tablet, slow release	17×4	F-6	¹¹¹ In	Yes	FA
T5	Osmotic pump	24×7	M-4	¹¹¹ In	No	FA
T6	Capsule, non-disintegr.	25×9	F-5C	^{99m} Tc	No	FA
T7	Tablet, slow release	2.5 diam.	M-4	^{99m} Tc	Yes	LB
T8	Tablet, non-disintegr.	12.0 diam.	M-8	¹¹¹ In	No	LB
T9	Osmotic pump	24×7	M-6	¹¹¹ In	No	LB
T10	Tablet, slow release	17×4	F-6	¹¹¹ In	Yes	LB
T11	Tablet, slow release	17×4	M-6	¹¹¹ In	Yes	LB
T12	Tablet, slow release	10.5	M-6	^{99m} Tc	Yes	LB
T13	Tablet, non-disintegr.	8.0 diam.	M-6	¹¹¹ In	No	VA
T14	Tablet, non-disintegr.	8.0 diam.	M-4	¹¹¹ In	No	HB
T15	Tablet, non-disintegr.	12.0 diam.	M-8	¹¹¹ In	No	HB
T16	Tablet, non-disintegr.	17×4	M-4	¹¹¹ In	No	HB
T17	Osmotic pump	24×7	M-6	¹¹¹ In	No	HB
Solution and dietary fibre (data from Malagelada <i>et al</i> ¹⁷)						
F1	Solution	—	6	^{99m} Tc	No	SM
F2	Fibre-cellulose	1-5	6	¹³¹ I	No	SM

M—male, F—female, D—diarrhoea, C—constipation, FA—fasted, LB—light breakfast (~1500 kJ), HB—heavy breakfast (~3600 kJ), VA—variable meal, SM—standard meal (800 kJ).

established by viewing the full sequence of images and by reference to a radiolabelled external marker taped to the skin overlying the liver to the right of the stomach. Many of the dosage forms provided good images of the various regions of the gastrointestinal tract, because they were solutions or multiparticulates, or the dosage form itself released activity. Representative images have been presented previously.^{17 18 20}

In some studies two dosage forms – for example, a single unit and pellets, labelled with different radionuclides were administered simultaneously, so that the stomach and colon images provided by the disperse system could be used to define the position

of the non-dispersed single unit.^{18 19} Transit times for non-disintegrating single unit systems were obtained directly by viewing the images. For solutions and multiparticulate systems the radioactivity in a given region of interest was quantified, corrected for background counts and radioactive decay and then pairs of anterior and posterior count rates were used to calculate geometric mean count rates.²¹ If two radionuclides were used simultaneously, then a correction was made for 'scatter-down' of the higher energy radiation (indium-111) into the energy window of the lower energy tracer (technetium ^{99m}).^{18 19}

The transit behaviour of the solution and multi-

particulate system has been expressed in terms of the time for half of the tracer to leave the stomach, or to arrive at the caecum. A small intestine transit time has been calculated as the difference between these two figures.

Results

The data from the various studies carried out with the different pharmaceutical dosage forms are listed in the Table and summarised in graphical forms in Figures 1 and 2 for gastric emptying and small intestinal transit respectively. During studies O and W gastric emptying of the single unit had not occurred in all subjects at the times of recording the last image, and these last times have been used in the calculation of the mean values.

GASTRIC EMPTYING

The gastric emptying of different physical forms varied according to the feeding conditions. Solutions and small pellets (less than 2 mm in size) emptied

from the stomach quite rapidly and were not greatly affected by the digestive state of the individual.

The emptying of the large single unit systems was greatly influenced by the presence of food in the stomach. In a fasted state rapid emptying was often observed, but even a light breakfast delayed emptying. A heavy breakfast resulted in greatly delayed emptying and in one study the units were retained in the stomach in all six subjects for at least nine hours (study T17). When subjects were allowed to choose a varied breakfast gastric emptying ranged from rapid (no breakfast) to very slow (heavy breakfast). No difference has been found between old and young subjects (studies T1, T4, T10 and T11 respectively).

SMALL INTESTINAL TRANSIT

When the equivalent data for small intestine transit are examined a very different picture emerges (Fig. 2). There were no differences that could be attributed to dosage form, or stomach contents. Indeed if the data for the three dosage forms are grouped

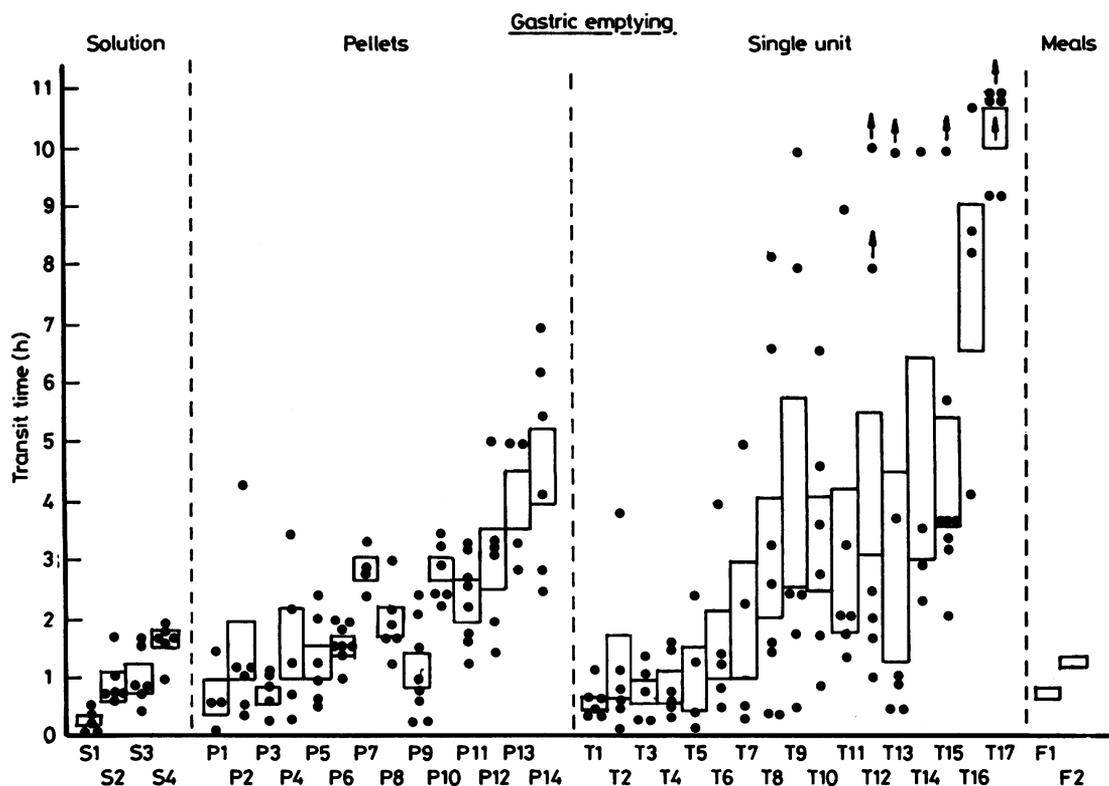


Fig. 1 Gastric emptying of pharmaceutical dosage forms. Individual data points as filled circles. Mean \pm SEM.

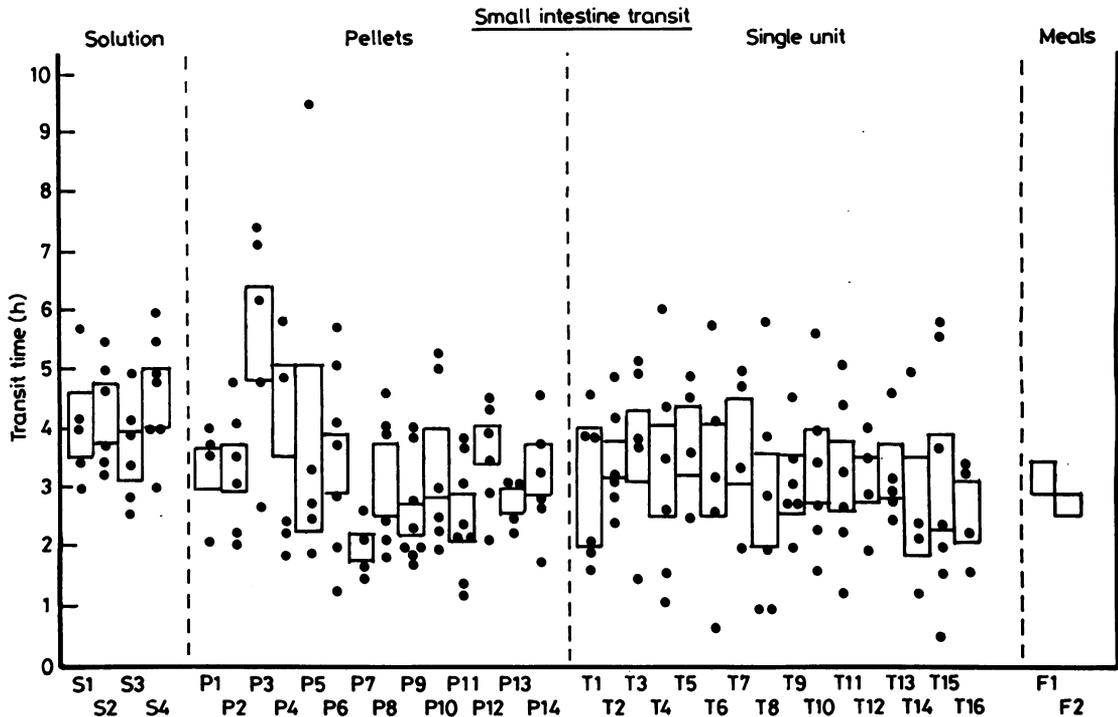


Fig. 2 Small intestinal transit of pharmaceutical dosage forms. Mean \pm SEM.

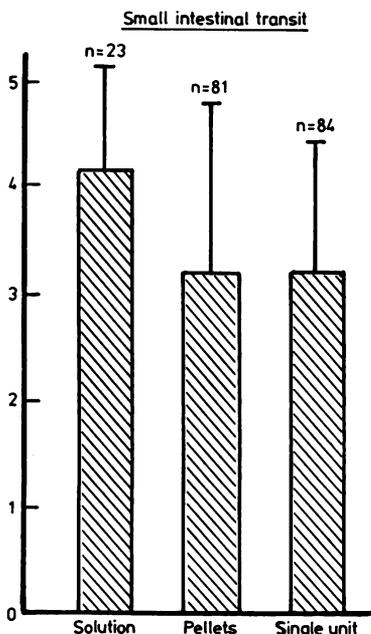


Fig. 3 Small intestinal transit of pharmaceutical dosage forms. Mean values \pm SD.

(Fig. 3) then there is no statistical difference in transit behaviour for solutions, pellets and single units. Not only were the differences between the various studies small but also the variation of transit times within a study was reduced for the single units. Somewhat surprisingly, the mean intestinal transit values for fasted subjects were not statistically different from those where the subjects received meals. It is appreciated that fasted subjects received a meal about three hours into the study and this would then change their digestive state. Most subjects, however, had rapid gastric emptying (< one hour) in the fasted state.

There was no difference that could be attributed to age in the small group of elderly subjects investigated.

Discussion

It has been shown that transit through the small intestine in healthy subjects is much more consistent than gastric emptying and it does not appear to be influenced by the physical state, or the size of the dosage form, nor by the presence of food in the stomach. The mean transit time of about three to

four hours agrees with the recent studies on the transit of food (mean transit solid food = 3.6 ± 0.3 h, $n=15$)²² and water (4.0 ± 0.8 h).²³ This supports the proposal of Hofmann *et al*⁶ who suggested that 'drugs, whether present as a particular dispersion, or as a micellar or molecular solution are considered to be propelled along the small intestine at the same net propulsive rate as food particles'. The recent work of Malagelada *et al*¹⁶ is also relevant. They found that a solution (labelled with ^{99m}Tc-DTPA) and a non-digestible solid particles of ¹³¹I-labelled fibre, gastric emptying was dependent on the physical nature of the test system, while small intestinal transit was not. They concluded that physiological discrimination between solids and liquids took place in the stomach, but not in the small bowel. Their mean values for small intestinal transit (3.0 ± 0.28 h solution and 2.7 ± 0.33 h solid) agree well with those given in the present report for a range of dosage forms.

The shortest small intestinal transit time found in the present work is of the order of 1.3 h, while the longest is about six hours. One individual had a value of nine hours the reason for this slow transit is not known.

IMPLICATIONS FOR DELIVERY THROUGH THE ORAL ROUTE

The concept that a pharmaceutical dosage form has on average about eight hours for transit in the small intestine is clearly incorrect in young healthy male subjects. The 95% confidence limit⁶ for the small intestine transit time which is equal, or less than that of 95% of healthy volunteers (SITT95) applied to the data in Figure 3 indicates that SITT95 would be about one hour. If a drug is absorbed exclusively from the small intestine there is a good chance that the time the delivery system spends in that region could be as short as one to two hours. Thus efficient disintegration of the dosage form and dissolution of the drug in the stomach could be a considerable advantage, if the stability characteristics of the drug so permit. In contrast, an over effective delay of a drug release such as enteric coating, could result in markedly decreased biological availability. Thompson *et al*,²⁴ however, have demonstrated variations in plasma glucose concentrations after oral dosing resulting from differences in motor activity in the upper gastrointestinal tract.

A number of recently developed controlled, or sustained release products claim steady drug release characteristics *in vitro* of between 12 and 24 hours. The relevance of such release profiles in clinical use can be questioned if the drug is absorbed only from the small intestine,²⁵ or is erratically absorbed from the large intestine,²⁶ or suffers significant biotrans-

formation by bacterial flora. If the delivery system reaches the caecum in three hours, then the greater proportion of the drug will be delivered not to the required site of the small intestine, but to the large intestine. Bioavailability data showing that the single dose controlled release system is equivalent to multiple doses of the drug over the same time scale and under fasted and non-fasted conditions, for subjects with long and short total transit times, would seem to be a sensible requirement for a satisfactory product to meet.

The retention of the dosage form in the stomach (for example after a meal) would be expected to provide a greater opportunity for drug absorption. Indeed clear advantages would be gained if dosage forms could be held in the stomach by being of low density (floating capsules)²⁷ or having so-called mucoadhesive properties.²⁸ The limited data presently available on these developments, however, suggest that these approaches are likely to have limited success. Taking a tablet sized, non-disintegrating single unit dosage form with a meal would have definite advantages. While the dosage form might remain in the stomach, the released drug would empty from the stomach with fluids and small food particles and be available for absorption from the intestine.¹⁰

The predictable nature of intestinal transit for pellet and single unit dosage forms (approx 3 ± 1 h, mean \pm SD) and the lack of an effect attributable to nutritional state means that it should be possible to design delivery systems for positioned release in the colon for the treatment of local conditions, such as ulcerative colitis.

It should be remembered that majority of the data discussed above have been obtained in a large group of healthy male young subjects who were able to take moderate exercise during the studies. It is known that certain disease conditions, such as inflammatory lesions, or disorders of gut motility can affect transit,^{12 29 30} as can the presence of administered drugs and unabsorbed food.¹² Similarly, in patients with partial obstruction or narrowed lumen, the passage of a single unit formulation may be impeded.³¹

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