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Gastrointestinal transit of dosage forms in the pig

S. S. Davis, L. Illum and M. Hinchcliffe

Abstract

The gastrointestinal transit of liquid, pellet and tablet formulations was measured under fasted conditions in the domestic pig (n = 4) using the technique of gamma scintigraphy.

The mean times for 50 % gastric emptying for liquid and pellet systems were 1.4 and 2.2 h, respectively; tablets emptied between 1.5 and 6.0 h. Total transit times were in the order of 50 h. These data conform well to published values for the transit of liquid and solid food materials in the pig. The times are much shorter than those previously published for the transit of solid dosage forms in the pig.

We conclude that the domestic pig would be a good model to study the gastrointestinal transit of pharmaceutical formulations and the absorption of drug compounds.

Institute of Pharmaceutical Sciences, Boots Science Building, University of Nottingham, Science Road, University Park, Nottingham, NG7 2RD, UK

S. S. Davis

West Pharmaceutical Services, Drug Delivery and Clinical Research Centre Limited, Albert Einstein Centre, Nottingham Science and Technology Park, Nottingham, NG7 2TN, UK

S. S. Davis, L. Illum, M. Hinchcliffe

Correspondence: S. S. Davis, Institute of Pharmaceutical Sciences, Boots Science Building, University of Nottingham, Science Road, University Park, Nottingham, NG7 2RD, UK.

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Introduction

Animal models are valuable for the evaluation of the gastrointestinal absorption of new chemical entities and the performance of novel dosage forms. The rat is considered to be a good model for studying the absorption of drug substances (Gardner et al 1996); however, due to its size, it is not suitable for investigations on oral dosage forms intended for administration to man. The dog has been considered by many groups as a popular model, but unfortunately the gastrointestinal tract is not physiologically comparable with that of man (Gardner et al 1996). The pig is considered to be the most suitable non-primate animal model since it resembles the human situation better than any other non-primate animal species with regard to eating behaviour, anatomy and physiology of the gastrointestinal tract (Fleming & Arce 1986; Kararli 1995). In the pig, each section of the gastrointestinal tract is comparable with that of man. Moreover, the bacterial flora of the colon and the digestion characteristics of the small intestines are considered to be similar to man (Dressman & Yamada 1991; Rowan et al 1994). The pig is currently used by different groups to evaluate a range of pharmaceutical dosage forms in bioavailability studies (Hildebrand et al 1991; Larsen et al 1992).

Information on gastrointestinal transit in the pig (minipigs and farm pigs) is sparse, although it is known that pigs possess an interdigestive migrating myoelectric complex similar to that in man (Rukerbusch & Bueno 1976). The small intestinal transit time is also thought to be similar to that of man (Gardner et al 1996), but long gastric emptying times have been reported (Hossain et al 1990; Aoyagi et al 1992). In particular, the gastrointestinal transit times of high, medium and low density non-erodible rigid oral dosage forms of large, medium and small sizes were reported to range from 2 to 33 days in the pig, as measured by roentgenography. Such transit times are extraordinary and at variance with studies on the emptying

of food from the pig stomach (Gregory et al 1990; Potkins et al 1991; Johansen et al 1996), and if correct, could well limit the use of the pig for studying the oral absorption of drugs.

Previously, when studying the gastrointestinal transit of dosage forms in man, we have made good use of the technique of gamma scintigraphy. Herein, the dosage form is labelled by a suitable gamma-emitting radionuclide and its passage through the different regions of the gastrointestinal tract followed using a gamma camera (Davis et al 1992). We now have available a dedicated facility for studying the gastrointestinal transit of dosage forms in large animal models such as the pig. Importantly, the pigs can be imaged in a non-sedated state since it is known that sedation (and anaesthesia) can slow down transit in the pig (Nimmo 1989).

This paper describes some preliminary studies on the gastrointestinal transit and, particularly, gastric emptying of liquid and solid dosage forms in the pig model, using labelled dosage forms and gamma scintigraphy.

Materials and Methods

Materials

A technetium-99m (Tc-99m) tin colloid solution (approx. 150 MBq mL^{-1}), used to follow the gastric emptying of a liquid formulation was supplied by the Department of Medical Physics, Queen's Medical Centre, Nottingham, UK. This solution was used to prepare a solution containing 5 MBq mL^{-1} radioactivity for administration to the pigs. Two solid dose oral formulations, a pellet and a tablet, were prepared.

Pellet preparation

Amberlite ion exchange resin (400 mg) (IR 120; Sigma Chemical Co., UK) with a diameter of 0.85–1.4 mm wet sieve size was labelled with indium-111 (In-111) using indium chloride (Department of Medical Physics, Queen's Medical Centre, Nottingham, UK) and filled into size 0 gelatin capsules to provide 0.5 MBq per capsule at the time of dosing.

Tablet preparation

Non-disintegrating capsule-shaped tablets ($22.0 \times 8.7 \times 5.1$ mm) were prepared from a mixture of lactose (70%) (Zeparox; Borcule Whey Products UK) and Avicel (29%) (Honeywill and Stein), on a Manesty F3 tablet press using size 0 caplet-shaped punches and dies. Magnesium stearate (1%) was used as a lubricant. The tablets were film-coated using a 3% solution of ethylcellulose in ethanol (Ethocel; Dow Chemical UK), using an Aeromatic STREA-1 film-coater. The tablets were radiolabelled using an In-111 Amberlite IRP-69 complex. Such labelling was performed by drilling a hole (approx. 2 mm diam. $\times$ 2 mm deep) into the tablet and adding 10 mg of the Amberlite complex. The hole was sealed with cyanoacrylate adhesive (Superglue; Loctite, UK). The surface area covered by the adhesive was slightly greater than that of the hole although this did not affect the overall dimensions of the tablet. The total dose of radioactivity was approximately 0.5 MBq at the time of dosing.

Animals

Four female pigs (large white/Landrace/Duroc cross), approximately 90–100 kg, were housed in individual pens located in an environmentally-controlled room and kept under 12-h continuous light and 12-h darkness at 19–22°C. The pigs had been previously prepared with a fistula inserted in the terminal ileum and venous access port as described by Gardner et al (1996). The pigs were fed twice a day with a standard grower diet and were given free access to water. For the study, the pigs were fasted overnight (approx. 18 h) and were fed approximately 6 h after dosing. During dosing, the pigs received a light meal in the form of a milkshake drink. During the course of the study day, the pigs were restrained in metabolism crates for gamma camera imaging. Between images, the pigs were returned to their housing pens. The pigs had been trained over a period of approximately 12 weeks and were used to handling and being kept for periods of time in the metabolism crates to minimize possible stress.

Dosing

A two-way crossover study was performed. There was a five-day washout period between successive dose administrations. Two pigs received the tablet formulation and two pigs received the pellet preparation followed by a drink containing Tc-99m on each study day. The solid dosage forms were administered directly to the back of the oral cavity by hand. Immediately after the administration of the solid dosage form, the pigs were given a drink of 200 mL strawberry milkshake (Sainbury's,

UK), containing 5 mL of the 5 MBq mL^{-1} Tc-99m tin colloid solution (25 MBq total).

Scintigraphic measurements

On each study day, two anatomical markers (In-111) were attached to each side of the pig using adhesive tape to act as reference points during the scintigraphic imaging and analysis. The markers were positioned in the dorsal regions of the mid-to-lower trunk immediately before dose administration. An area of skin was shaved to facilitate the attachment of the markers. A permanent marker pen was used to record the position of the markers on the skin for relocation in further imaging. The pigs were placed in front of a single-headed gamma camera (GE Maxi-Camera) with a 40-cm field of view, fitted with a medium energy collimator. The camera was tuned to record separate images for the indium and technetium radionuclides.

A right and left lateral view image of the mid-to-lower trunk of each pig was collected at each time point. Right lateral view images were collected for Tc-99m and then In-111 before collecting left lateral view images for each isotope. The time taken to reposition the pigs between imaging on right and left sides was approximately 30 s. Static images (30 s) were collected immediately after dosing and then at approximately 15, 30, 45, 60, 90, 120, 180 and 240 min. For the tablet formulations, additional images were collected at 300 and 360 min. Subsequent images were collected at 24, 48, 72 and 96 h after dose administration. The imaging times and duration of imaging were based on observations of the gastric emptying and transit characteristics of the various dosage forms at the time of imaging.

Data analysis

Gamma camera images were analysed as previously described for studies on human subjects (Perkins 1999). Regions of interest that corresponded to the stomach were created so that gastric emptying time could be measured. Due to the convoluted nature of the gastrointestinal tract of the pig it was difficult to create well-defined regions of interest for the small intestine and colon. Total transit was measured by imaging the pigs until activity in the indium channel had returned to background levels. The activity (counts per cell) in the right and left lateral regions of interest, corrected for both background activity and radioactive decay, was used to determine the average activity at each time point. The average activity at Time 0 was used to denote the total activity. For each subsequent image, the average activity was expressed as a percentage of the total activity. No correction was made for down-scatter due to co-administration of the two radionuclides.

Table 1 Gastric emptying of a liquid formulation of Tc-99m in pigs.

Time (min)	% counts relative to total		
	Day 1 (n = 4)	Day 2 (n = 4)	Days 1 and 2 (n = 8)
0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
15	97.1 ± 16.8	96.5 ± 19.7	96.8 ± 16.9
30	85.1 ± 15.5	79.6 ± 19.4	82.3 ± 16.5
60	82.8 ± 34.3	60.8 ± 23.1	71.8 ± 29.5
90	50.4 ± 21.5	56.0 ± 27.1	53.2 ± 22.9
120	41.9 ± 12.9	43.9 ± 16.0	42.9 ± 13.5
180	26.6 ± 13.2	36.6 ± 22.4	31.6 ± 17.8
240	26.4 ± 16.3	32.2 ± 15.4	29.3 ± 15.0

Data are mean ± s.d.

Table 2 Gastrointestinal transit of a pellet formulation (Amberlite in gelatin capsule) in pigs.

Time (min)	% counts relative to total
0	100.0 ± 0.0
15	83.5 ± 22.7
30	71.7 ± 25.0
60	62.2 ± 19.1
90	67.6 ± 26.1
120	49.1 ± 24.4
180	51.0 ± 23.7
240	40.8 ± 19.8

Data are mean ± s.d.

Results

Gastric emptying

Data on the gastric emptying of liquid and solid (pellet and tablet) formulations are shown in Tables 1–3.

Liquids

The four pigs received the liquid formulation on each study day (in combination with the administration of either the tablet or the capsule). Mean gastric emptying profiles obtained from the combined data are shown in

Table 3 Gastrointestinal transit of a tablet formulation in pigs.

Pig no.	Gastric emptying (h)	Total transit through the gastrointestinal tract (h)
1	5.0–6.0	> 72 < 96
2	–[a]	> 24 < 48
3	5.0–6.0	> 24 < 48
4	1.5–2.0	> 24 < 48
t50 liquid Day 1 (n = 4)	1.6	–
t50 liquid Day 2 (n = 4)	1.3	–
t50 liquid Days 1 and 2 (n = 8)	1.4	–
t50 pellets (n = 4)	2.2	> 24 < 48

t50 is the mean time for 50 % emptying. [a]Pig bit tablet and swallowed fragments.

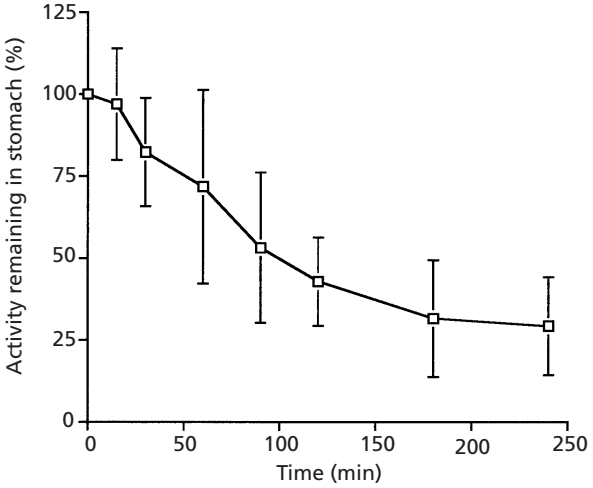

Figure 1 Mean gastric emptying of liquid formulations in pigs (n = 8).

Figure 1. Mean gastric emptying times for the two separate days were also plotted (data not shown), and the profiles were similar to that for the mean data shown in Figure 1. In some pigs there appeared to be a short lag phase before emptying of the liquid occurred. The mean time for 50 % emptying (t50) of the liquid was approximately 1.4 h (t50 = 1.6 and 1.3 h on Days 1 and 2, respectively; n = 8).

Pellets

Data describing the emptying of pellets administered in a hard gelatin capsule from the fasted stomach of the pig are shown in Table 2 and Figure 2. Figure 2 indicates that the gastric emptying consists of a rapid phase

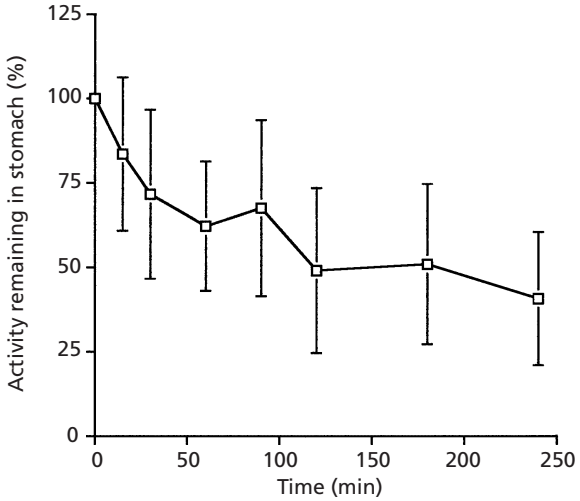

Figure 2 Mean gastric emptying of pellet formulations in pigs (n = 4).

followed by a slower phase. The profiles are generally similar to those found for the liquid marker. The t50 was also similar to that found for the liquid system (2.2 h).

Tablets

Only three values for the gastric emptying of the tablet formulation were available (Table 3), as in one instance the pig bit the tablet and swallowed the fragments and consequently a gastric emptying time could not be obtained. The time for gastric emptying was recorded as the interval when the tablet was found in the stomach region and then in the intestinal region. In two pigs the tablet emptied between 5 and 6 h, whereas in the third pig, gastric emptying occurred between 1.5 and 2 h.

Small intestinal transit

As mentioned above, it was difficult to quantify the transit of the different dosage forms from the stomach through the small intestine to the ileocaecal junction due to the complex anatomy of the pig intestines. An estimate based on transit rate and stagnation (apparently at the ileocaecal junction) could be made which indicated that the transit of the various dosage forms through the small intestine was approximately 3–4 h.

Total transit

The use of a short half-life radionuclide in the form of Tc-99m did not allow the determination of a total transit time for the solution formulation. The pellets, labelled with In-111, had a total transit of > 24 < 48 h, whereas

Table 4 Studies on gastric emptying in fed and fasted pigs.

	Gregory et al (1990)	Treacy et al (1990)	Johansen et al (1996)	Potkins et al (1991)	Weber & Ehrlein (1998)	Present study
State	Fed	Fed	Fed	Fed	Fed	Fasted/ light meal
Liquid marker	0.9–1.3	0.4	1.2	–	–	1.4
Solid marker	3.0–4.5	–	2.5	3.8–5.5	4.9	2.2 (pellets)
						1.5–6.0 (tablets)

Data represent the mean time for 50% emptying of a marker (h).

the tablet formulations also labelled with In-111 were $> 24 < 48$ h for three pigs and $> 72 < 96$ h for the fourth pig (fragments seen in the pig that bit the formulation).

Discussion

The transit data obtained in pigs in this study are summarized in Table 4. The gastric emptying of solution and pellet formulations was from 1.4 to 2.2 h, whereas the emptying of tablets was between 1.5 and 6.0 h in the fasted pig. We believe that this is the first published report on the gastrointestinal transit of pharmaceutical dosage forms in the pig measured using the non-invasive technique of gamma scintigraphy. Wilding et al (unpublished results) have previously conducted preliminary investigations in the heavily-sedated pig. They used a 33-kg female pig that had been fasted for 12 h and found that a labelled solution (Tc-99m-labelled DTPA in 120 mL water) demonstrated initial rapid gastric emptying, but after 60 min gastric stasis appeared to occur which may be related to the use of a sedative. The t50 was approximately 1.9 h. The small intestinal transit was in the region of 4 h.

The gastric emptying of solutions and pellets (and possibly the single unit tablet formulations) determined in this work appears to be somewhat longer than that found in man. Typical values for the emptying of such dosage forms in man are as follows for the fasted stomach: 11 min for solutions (Adkin et al 1995; Wilding et al 1994); and 0.5–1.5 h for pellets and single units (Davis et al 1986).

Our data showing that liquids, pellets and tablets empty from the stomach of the fasted pig over periods of 1.4 to 6 h are in direct contrast with data obtained by Hossain et al (1990) who reported that a prolonged gastric residence (> 5 days) occurred with non-disintegrating caplets of different densities. The longest total gastrointestinal transit recorded in that study was 33 days. The animals received the dosage forms by intubation on an empty stomach (after 12 h fasting) and were, moreover, fasted 8 h after dosing. The caplets had densities of 1.25, 1.45 and 2.30 g mL^{-1} and were in three sizes: large (20 mm long $\times$ 10 mm diam.); medium (10 mm $\times$ 10 mm); and small (5 mm $\times$ 10 mm). Transit was measured by roentenography.

It is difficult to explain the dramatic difference in gastric emptying (up to 25-fold) between the results obtained in our study and those obtained by Hossain et al (1990). Although the formulations studied by Hossain et al (1990) were in general denser than those in our study, it is surprising that density should make such a dramatic difference. Devereux et al (1990) examined the gastric emptying, intestinal transit and caecum arrival times of 1-mm pellets with a of density 1.5 and 2.8 cm^{-3}, in fed and fasted volunteers using gamma scintigraphy. The higher density pellets had a somewhat extended residence time in both the fed and fasted states, and gastric emptying was prolonged in the fed state (e.g. t50 for light particles (fasted) = 125 min; heavy particles (fasted) = 204 min). However, such differences attributable to density do not explain the apparent anomaly between the data from our study and that of Hossain et al (1990).

We compared our data and those of Hossain et al (1990) with literature studies on the gastric emptying of liquid and solid markers from the pig stomach. Such studies have been undertaken in the field of nutrition using cannulated animals (Table 4).

The effect of feeding on the pattern of gastric emptying in the pig was investigated by Gregory et al (1990). Studies were performed in pigs fitted with a gastric cannula and fed a normal solid diet of finely ground material. Water containing CrEDTA was used as a

liquid marker. Gastric emptying was measured using a gastric evacuation technique. The emptying of both solid matter and liquid followed an exponential pattern after feeding but was linear when the animals were feeding. Their findings confirmed the earlier studies of Laplace & Tomassome (1970), which suggested that there was an initial phase of rapid gastric emptying followed by a prolonged phase of regular but slower emptying of a mixed solid–liquid meal. Typical values for t50 can be obtained from their results: liquid 0.9–1.3 h (depending on liquid volume, 1800 and 3010 mL, respectively); solid matter 3–4.5 h (depending on quantity, 783 or 1305 g, respectively).

Pyloric motor function during the emptying of a liquid meal from the stomach in the conscious pig was described by Treacy et al (1990). Gastric emptying was measured by drainage of the proximal duodenum through a cannula. Radiolabelled dextrose (1000 mL of a 5% solution) was used and the relative volumes emptied from the duodenal cannula were calculated every 5 min for a 30-min period after administration of the dextrose. Alteration of emptying was produced by infusion into the more distal duodenum of nutrient and non-nutrient solutions of differing osmolality. In control pigs ($n = 6$), the volume of liquid emptied after 30 min was 739 mL (range 642–929 mL). Their findings suggested a major role for the pylorus in the control of emptying of liquids from the pig stomach, both as a component of an antro-pyloric peristaltic pump and as a resister to transpyloric flow during stimulation of duodenal receptors by nutrients and non-nutrients. The authors considered that there was a close similarity between the pyloric motility in pigs and that in man.

Johansen et al (1996) studied the effects of varying content of soluble dietary fibre from wheat flour and oat milling fractions on gastric emptying in pigs fitted with a gastric cannula. Gastric contents were collected 0.5, 1, 2, 3 or 5 h after a morning feed. PEG 400 was used as a liquid phase marker and chromic oxide as a solid phase marker. The t50 of these markers can be estimated from their data to be 1.2 and 2.5 h, for liquid and solid phases, respectively. Potkins et al (1991) investigated the gastric emptying rate and rate of passage of digesta to the terminal ileum and through the whole of the gastrointestinal tract in 12 cannulated pigs using chromic oxide as a marker. Gastric emptying was characterized by a first order process from which rate constants for emptying were obtained. The following values are of interest: gastric emptying (t50) was 3.8–5.5 h and total transit was 24.8–40.9 h, depending on the nature of the administered polysaccharide diet. The time for the passage of the bulk of the digesta to the terminal ileum varied from 6.6 to 8.0 h, again depending on the nature of the administered diet.

Gastric emptying in minipigs (45–60 kg; $n = 4$) was measured by Weber & Ehrlein (1998). Jejunal cannulation was used to follow emptying and cobalt-EDTA was used as a non-absorbable marker. Different meals had a volume of 1000 mL and a calorie load of 1 kcal mL^{-1}. Gastric emptying rate expressed in terms of energy was 1.70 ± 0.53 kcal min^{-1} and was not significantly different despite large differences in meal composition. This result provides a t50 value of 4.9 h for gastric emptying.

It can be seen from Table 4 that the various values for the gastric emptying of solid and liquid markers in fed pigs obtained from the literature are not dissimilar to those found in this work for different pharmaceutical formulations, bearing in mind that the previous studies were performed in fed rather than fasted animals. There is no suggestion from these studies in the field of nutrition that gastric emptying in the pig can be of the order of days.

Conclusions

This study on the gastrointestinal transit of pharmaceutical formulations in the fasted pig using gamma scintigraphy showed that gastric emptying is somewhat slower than that found in man, but that small intestinal transit and total transit seem to be similar to those found in man. Therefore, the pig can be considered to be a suitable model for the evaluation of the performance of oral pharmaceutical products.

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