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The fate of multiple-unit enteric-coated formulations in the stomach of the dog

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Summary

The gastrointestinal transit of enteric granules was studied in healthy dogs and in a dog suffering from pancreatic insufficiency by means of roentgenography. Coated granules of different sizes were given to the dogs during the main meal or with a small portion of food before the meal. The enteric materials used were hydroxypropyl methylcellulose phthalate (HPMCP) and cellulose acetate phthalate (CAP). The majority of enteric granules with a diameter of 0.3–1 mm and 1–1.7 mm remained in the stomach for up to 6–8 h. Reduction in granule size and the time of adding the drug to the food were shown to have no significant effect on the gastric emptying of these granules. The formulations were emptied from the stomach much later than food, and it is therefore highly questionable whether this particular dosage form is suitable for the treatment of pancreatic insufficiency in dogs. A special type of controlled-release granule was developed, using HPMCP as a coat (7%) and potato starch as a disintegrant in the core. This formulation disintegrated in front of the pylorus 1–2 h after drug administration, showing an almost ideal release of the drug suitable e.g. for pancreatic enzyme therapy. However, further development is necessary.

Introduction

Pancreatic insufficiency is a disease in which the quantity of enzymes released from the pancreas is remarkably reduced. This results in an inadequate amount of pancreatic enzymes in the small intestine and causes malabsorption of food. Primary treatment consists of pancreatic enzyme supplementation via administration of enteric-coated preparations containing acid-labile pancreatic extracts. However, in clinical situations numerous difficulties are encountered with this kind of therapy, especially concerning single-unit formulations (Graham, 1977; Ihse et al., 1980).

In our previous study (Marvola et al., 1986), it was also suggested that single-unit enteric preparations were not suitable for the veterinary drug therapy of pancreatic insufficiency. Enteric-coated barium sulphate capsules and tablets used as model preparations remained in the stomach of the dogs for up to 6–8 h when given with food. Owing to this prolonged period of time, the enzymes in the products never come into contact with food substrates in the small intestine. This is probably the main reason for the inadequate therapeutic effects of the single-unit pancreatic enzyme supplements.

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Several reports both in man and in dogs provide evidence that the gastric residence time of non-disintegrating dosage forms greatly depends on factors such as the presence of food in the stomach and the type and size of the dosage form administered. Hinder and Kelly (1977) and Meyer et al. (1979) demonstrated with dogs that digestible solids were ground to particles smaller than 2 mm in the fed state before being emptied from the stomach. Radio-opaque pellets and granules (1–3 mm) have been reported to be emptied from the stomach of dogs rapidly and randomly with the meal, while tablets and capsules were retained (Fara et al., 1985; Itoh et al., 1986). These larger objects were later emptied from the stomach during the strong muscular contractions of the interdigestive migratory myoelectric complex (IMMC or "housekeeper" wave).

The aim of the present study was to investigate the way in which enteric-coated granules behave in the stomach and in the intestine of both a healthy dog and a dog suffering from exocrine pancreatic insufficiency. The variables studied were: enteric coating material, coat thickness, granule size, use of a disintegrant in the core and timing of drug administration in relation to food ingestion.

Materials and methods

Preparation of barium sulphate granules

The granules were prepared from barium sulphate (Barisulf-HD, Leiras), lactose (Ph. Eur.) and potato starch (Ph. Eur.) as follows:

	A	B
Barium sulphate	33%	33%
Lactose	49%	44%
Potato starch	–	5%
Gelatin solution (20%)	18%	18%

In composition B potato starch was added to ensure disintegration of the granules in front of the pylorus.

The barium sulphate was blended with the lactose and potato starch in a turbula-mixer (Turbula, W.A. Bachofen) and moistened with gelatin solution. The moist mass was then granulated in an oscillator (Erweka G.m.b.H.) with a mesh size of 2 mm. The granules were dried overnight in a drying oven at 38 °C. Finally the dry granules were screened manually and those measuring 0.3–1 mm and 1–1.7 mm in diameter were selected for filmcoating.

Coating

The two coating solutions used were as follows: (1) hydroxypropyl methylcellulose phthalate, HPMCP (HP-50, Shin-Etsu Chemical), 8%; dichloromethane (E.Merck), 46%; ethanol (Alko), 46%. (2) Cellulose acetate phthalate, CAP (Eastman Kodak): for granules 0.3–1mm in diameter 5%; -for granules 1–1.7 mm in diameter 9% and acetone (E. Merck) 95% or 91%. The coatings were applied using a fluidized bed coating technique (Aeromatic Strea 1, Aeromatic AG). Each batch coated comprised 100–120 g of granules. The inlet air temperature was adjusted to 38 ± 1 °C for the HPMCP solution and to 30 ± 1 °C for the CAP solution. The outlet air temperatures were 29 ± 1 °C and 23 ± 1 °C, respectively. The pneumatic spraying pressure was kept at 1.4 bar and the air flow rate at 130 $m^3 h^{-1}$.

The theoretical amount of coating was calculated from the total weight of the granules. For enteric coatings the amount of coating was 70% and for other types 3%, 5% and 7% of the total weight of the granules.

Disintegration of film-coated granules

The disintegration test was carried out using the basket-rack assembly apparatus (Ph. Eur.) with 500 ml of 0.1 M hydrochloric acid (pH 1.2) and a phosphate/citrate buffer solution (pH 6.8) at 37 °C.

Experiments with dogs

Six adult dogs were used in the experiments. Three of the dogs were healthy male Finnish harriers, two were healthy female beagles and one was an Alsatian bitch suffering from exocrine pancreatic insufficiency. The dogs were fasted overnight for at least 10 h. A standard semisolid meal of commercial food was given the following morning. The drug products were given either by mixing into the whole meal or by mixing into a

small portion given roughly 30 min before the main meal. No additional food was given during the experiments, although free access to water was allowed. Multiple X-rays (X-Omat L, Kodak) were taken immediately prior to administration and subsequently at 0.25, 0.5, 1, 2, 3, 4, 5, 6 and 8 h. The accuracy of the timing was ± 5 min; larger deviations are mentioned separately.

Results

In vitro

The disintegration properties of the multiple-unit barium sulphate preparations studied are shown in Table 1. Enteric granules coated heavily with HPMCP or CAP (70% of the total weight of the granules) remained intact in 0.1 M hydrochloric acid (pH 1.2) for a period of 2 h. This was intended to study the gastric emptying of these dosage forms. The coated particles then disintegrated rapidly (15–20 min) in a phosphate–citrate buffer solution (pH 6.8).

The disintegration time of the coated B granules in vitro was 6–30 min in 0.1 M hydrochloric acid, close to the estimated time taken for the granules to reach the front of the pylorus.

In vivo

The behaviour of HPMCP-coated (70%) granules (1–1.7 mm) in the stomach of the sick dog is illustrated in Fig. 1. Following administration the granules were distributed fairly evenly throughout the stomach. At 1 h the majority had accumulated towards the antrum and during the following 3.5 h were seen to move to the front of the pylorus. By this time the greater part of the granules had been emptied from the stomach. It is clear that the HPMCP granules distintegrated rapidly in the upper part of the duodenum, since no granules were visible in the intestine. No adhesion to the gastric mucosa was observed. At 6.5 h the remaining granules were swept into the duodenum by the "housekeeper" wave, and at 9 h all HPMCP granules had disintegrated in the GI tract.

TABLE 1

The disintegration of the coated barium sulphate granules in vitro

Preparation	Film forming agent	Amount of coating, % of total weight of granules	Disintegration time (min)	
			pH 1.2	pH 6.8
Coated A granules	HPMCP	70%	>120	16
	CAP	70%	>120	20
Coated B granules	HPMCP	3%	6	–
		5%	10	–
		7%	30	–

The behaviour of similar granules in a healthy dog is shown in Fig. 2. The preparations were scattered throughout the stomach and descended towards the antrum remarkably slowly, taking roughly 3 h. At 5 h the granules had accumulated in front of the pylorus, their number having clearly diminished. Obviously during this period the majority of HPMCP-coated granules had either passed through the pylorus or had disintegrated in the stomach. As with the sick dog, no granules were seen in the intestine during the experiment.

A further study was carried out on the sick dog using CAP-coated granules (1–1.7 mm), the results of which are shown in Fig. 3. Here the amount of barium sulphate granules given to the dog was twice as high as in the previous experiment. At 15 min numerous particles were already visible in the duodenum, the quantity continuing to increase throughout the experiment. At 3.5 h the majority of granules had accumulated in the antrum and were still sharply outlined and uniform in shape. During the next 2 h a cluster was formed in front of the pylorus, and at 6.5 h a clear "housekeeper" motility pattern was observed, sweeping the granules into the duodenum. The CAP granules finally disintegrated in the large intestine, as clearly shown by the find X-ray at 7.5 h.

The experiment with CAP granules (1–1.7 mm) in a healthy dog is shown in Fig. 4. As with the sick dog, the granules remained scattered throughout the stomach for a prolonged period of time after ingestion. At 4 h those granules still in the stomach had accumulated in front of the pylorus. At 6 h the majority of granules had been emptied from the stomach and did not disintegrate until they reached the large intestine.

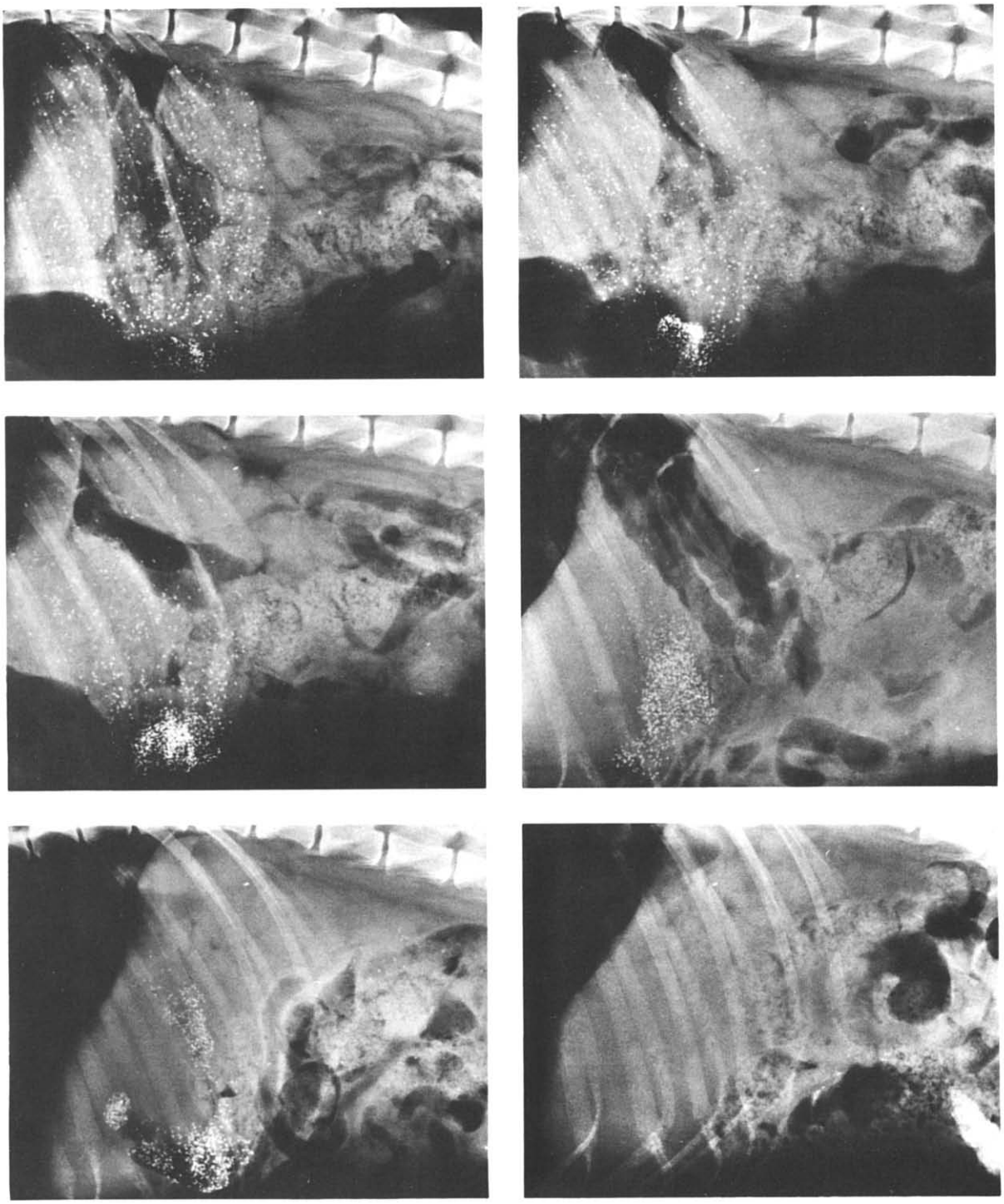

Fig. 1. X-rays showing the behaviour of HPMCP-coated (70%) granules (1–1.7 mm) in the stomach of a sick dog at 0.25, 0.5, 1, 4.5, 6.5 and 9 h.

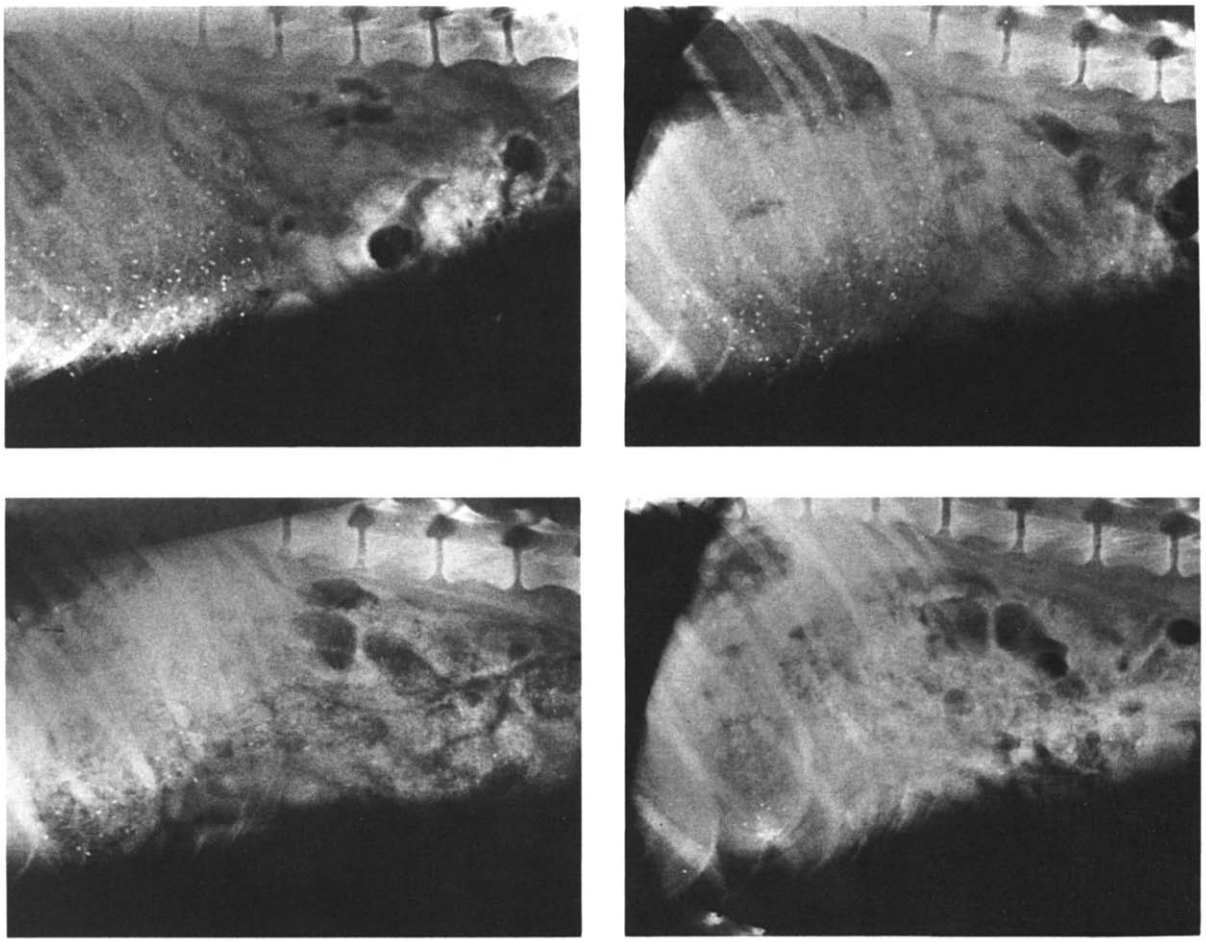

Fig. 2. X-rays showing the behaviour of HPMCP-coated (70%) granules (1–1.7 mm) in the stomach of a healthy dog at 0.25, 1, 3 and 5 h.

To examine the effect of granule size on gastric emptying time, the behaviour of small CAP-coated granules (0.3–1 mm) was studied both in the sick (Fig. 5) and in a healthy dog (Fig. 6). Both the distribution in the stomach and the gastric transport of these preparations were very similar to those of the larger granules. The gastric emptying times observed were 7 h in the sick dog and over 6 h in the healthy dog. Due to the very small size of these granules, it was rather difficult to distinguish them on the X-rays.

In the last experiment, HPMCP-coated granules with a disintegrant in the core were examined in healthy dogs. The amounts of coating used were 3%, 5% and 7% of the total weight of the granules. The granules were administered with a small portion of food roughly 30 min before the main meal. These preparations were designed to disintegrate in the stomach in front of the pylorus and to release the active ingredients through the pylorus in powdered form. Granules coated with 3% and 5% HPMCP rapidly disintegrated in the stomach, the majority still being distributed throughout the stomach. The disintegration times noted were 15 min and 35 min, respectively. The preparations coated with 7% HPMCP had accumulated in the antrum within 45 min, and partial disintegration was observed during the next 2 h (Fig. 7). At 5.5 h the granules had almost totally disintegrated in the stomach. The disintegration times of these

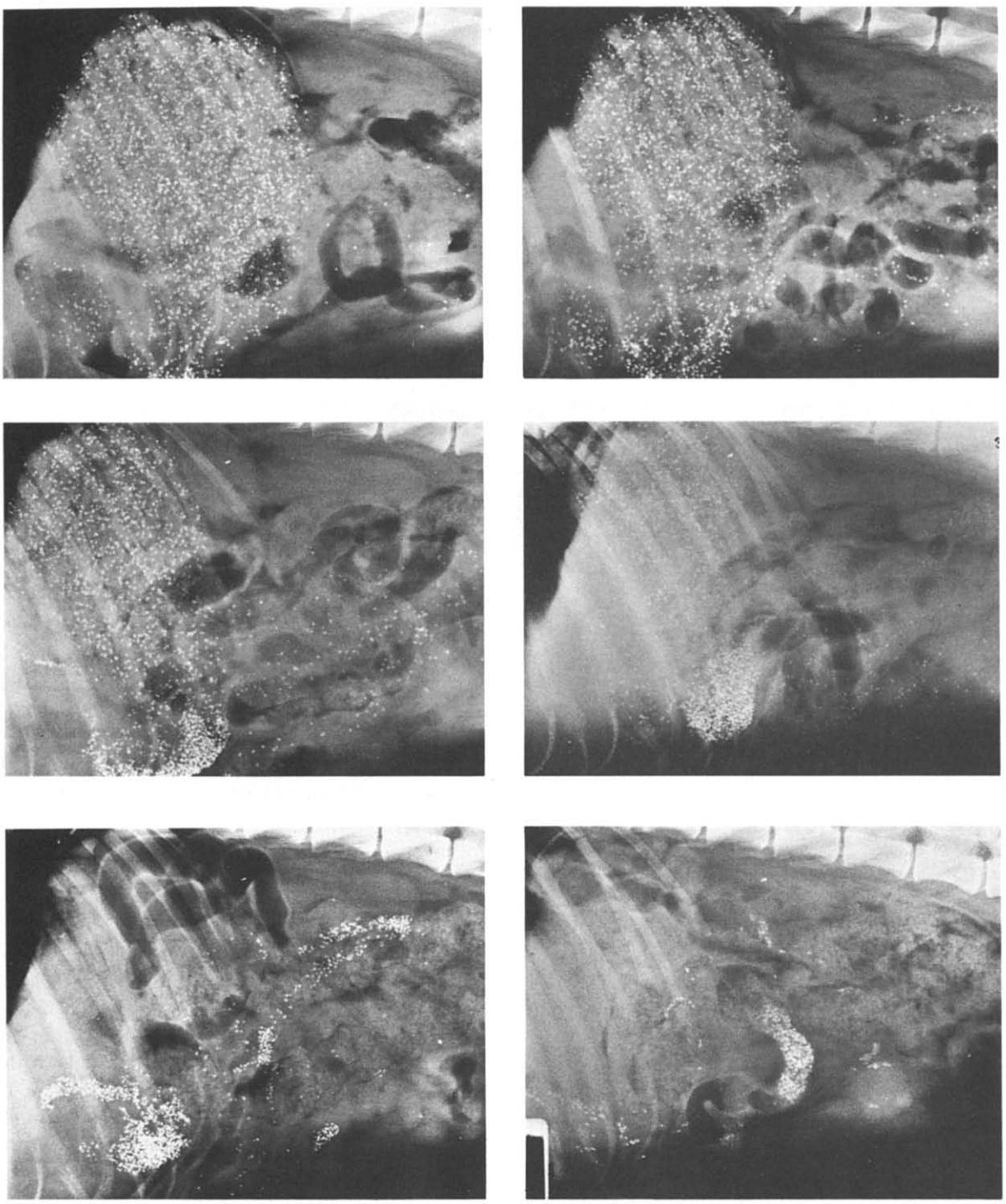

Fig. 3. X-rays showing the behaviour of CAP-coated (70%) granules (1–1.7 mm) in the stomach of a sick dog at 0.25, 1, 2, 3.5, 6.5 and 7.5 h.

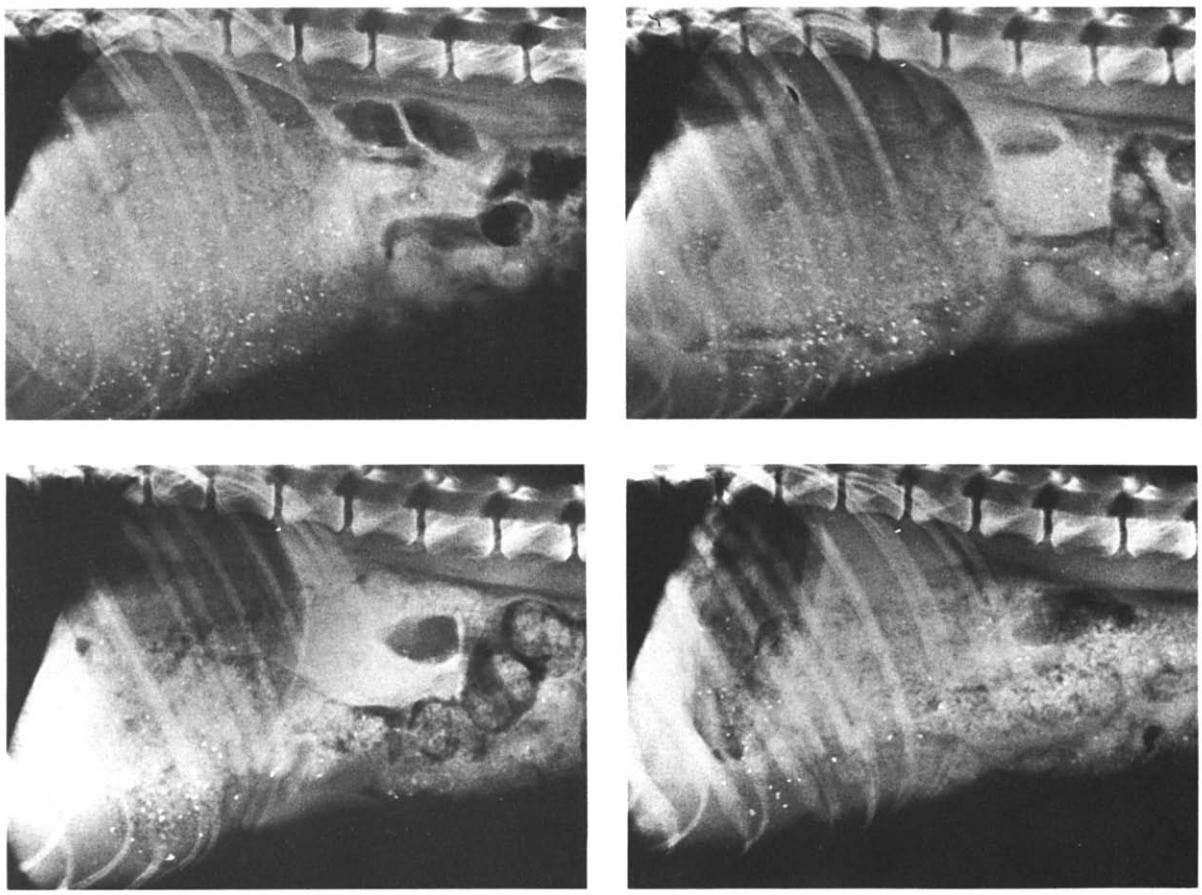

Fig. 4. X-rays showing the behaviour of CAP-coated (70%) granules (1–1.7 mm) in the stomach of a healthy dog at 0.25, 1, 4 and 6 h.

preparations in vitro were 6 min, 10 min and 30 min for coatings of 3%, 5% and 7%, respectively.

Discussion

Following administration, all multiple-unit enteric preparations were dispersed throughout the stomach of the dogs and accumulated remarkably slowly in front of the pylorus (Figs. 1–4). The accumulation time of these preparations was 3–5 h, regardless of whether the dog was healthy or suffered from pancreatic insufficiency. Very few studies have been published concerning the effect of such distribution on the gastric emptying of granules. As early as 1960, Wagner reported that optimum multiple-unit preparations would be those in which a large number of coated granules were contained in a capsule (Wagner et al., 1960). According to a recent publication, no significant differences in emptying time were found between predispersed granules and granules dosed in hard gelatin capsules (O'Reilly et al., 1987). From our results it can be concluded that the wide dispersion of granules delays the passage of these preparations into the duodenum.

According to the literature, digestible particles reduced to a size of 2 mm or less are emptied from the fed stomach of dogs both rapidly and randomly as liquids (Hinder and Kelly, 1977). As seen on Figs. 1–4, however, the majority of multiple-unit preparations in our study (1–1.7 mm in diameter) remained in the stomach of the dogs for up to 6–8 h before being swept into the duodenum

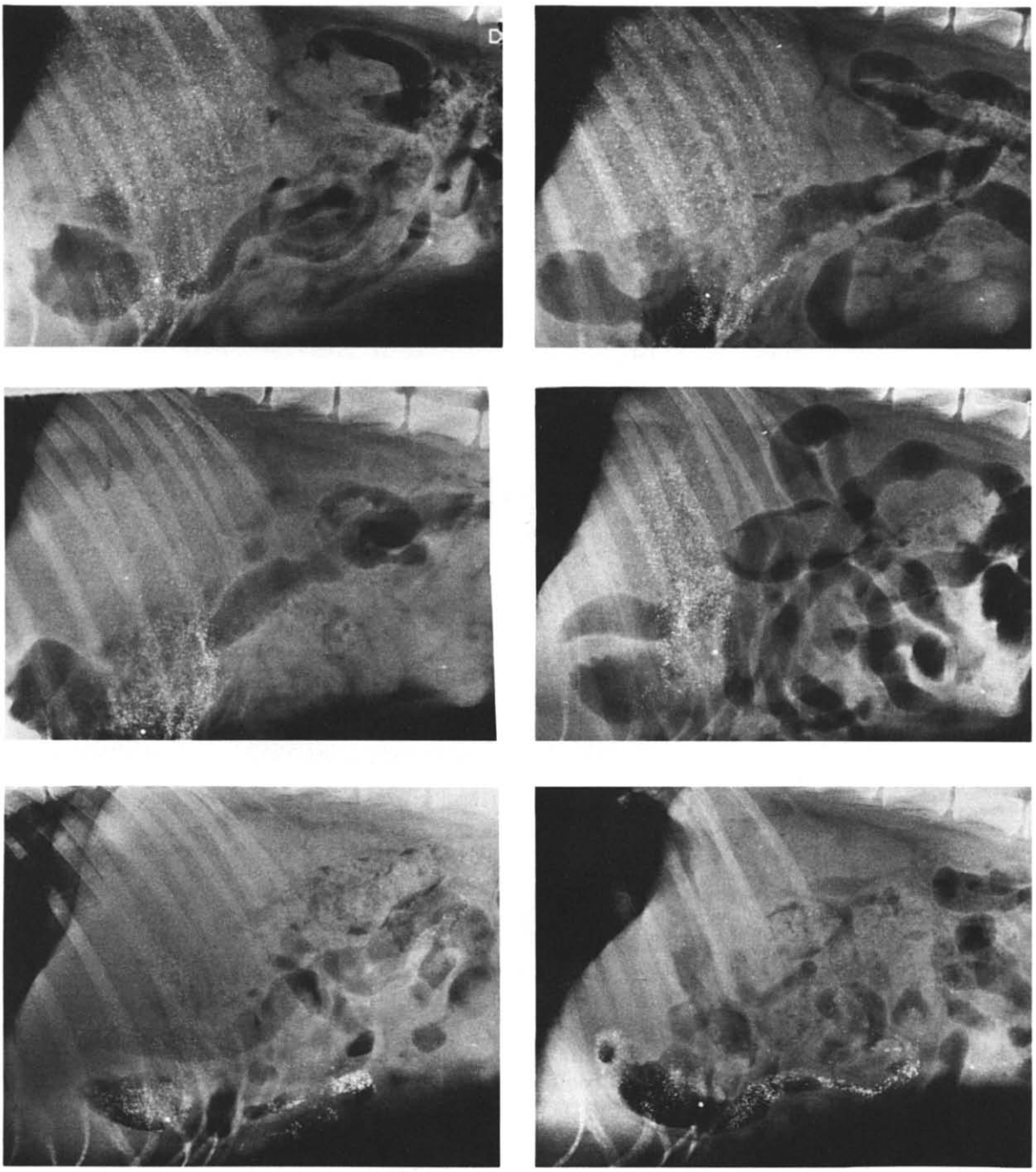

Fig. 5. X-rays showing the behaviour of CAP-coated granules (0.3–1 mm) in the stomach of a sick dog at 0.5, 1, 2, 5, 6 and 7 h.

by the powerful contractions of the "housekeeper" wave (Fig. 3). These findings indicate that granules 1–1.7 mm in diameter are not small enough to pass freely through the pylorus in the fed state. The granules clearly accumulated in front of the pylorus and were mostly emptied from the fed

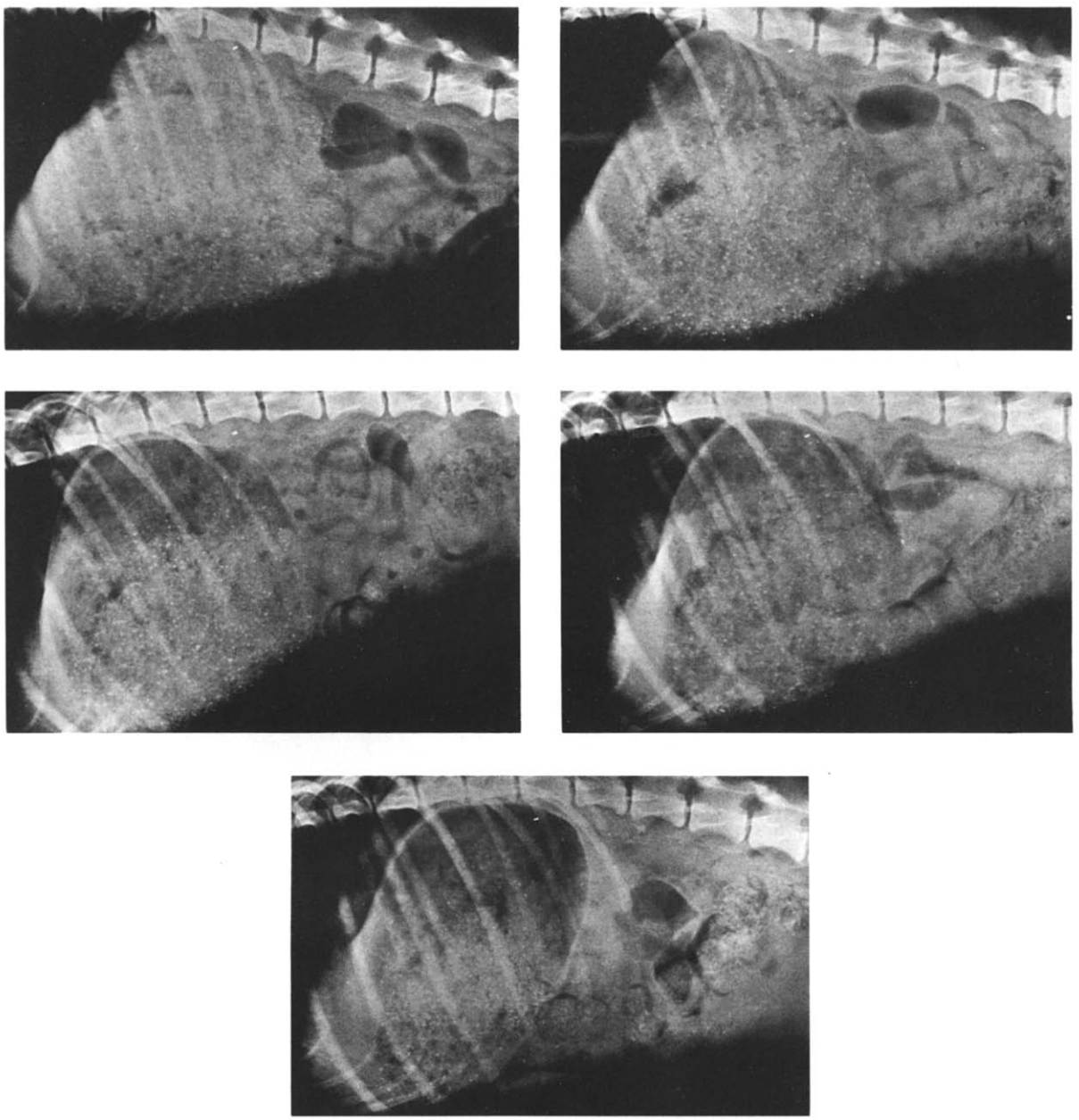

Fig. 6. X-rays showing the behaviour of CAP-coated granules (0.3–1 mm) in the stomach of a healthy dog at 0.25, 1, 2, 4 and 6 h.

stomach in a similar fashion to large single-unit preparations such as tablets and capsules (Marvola et al., 1986). It is clear that the majority of pancreatic enzymes prepared in granule form would never be emptied from the stomach simultaneously with food.

The reduction of granule size to 0.3–1 mm had no clear effect on the gastric-emptying time of these preparations (Fig. 5). The similar time for both granule fractions indicates that the majority of preparations passed through the pylorus have a particle size of less than 0.3 mm. This is also

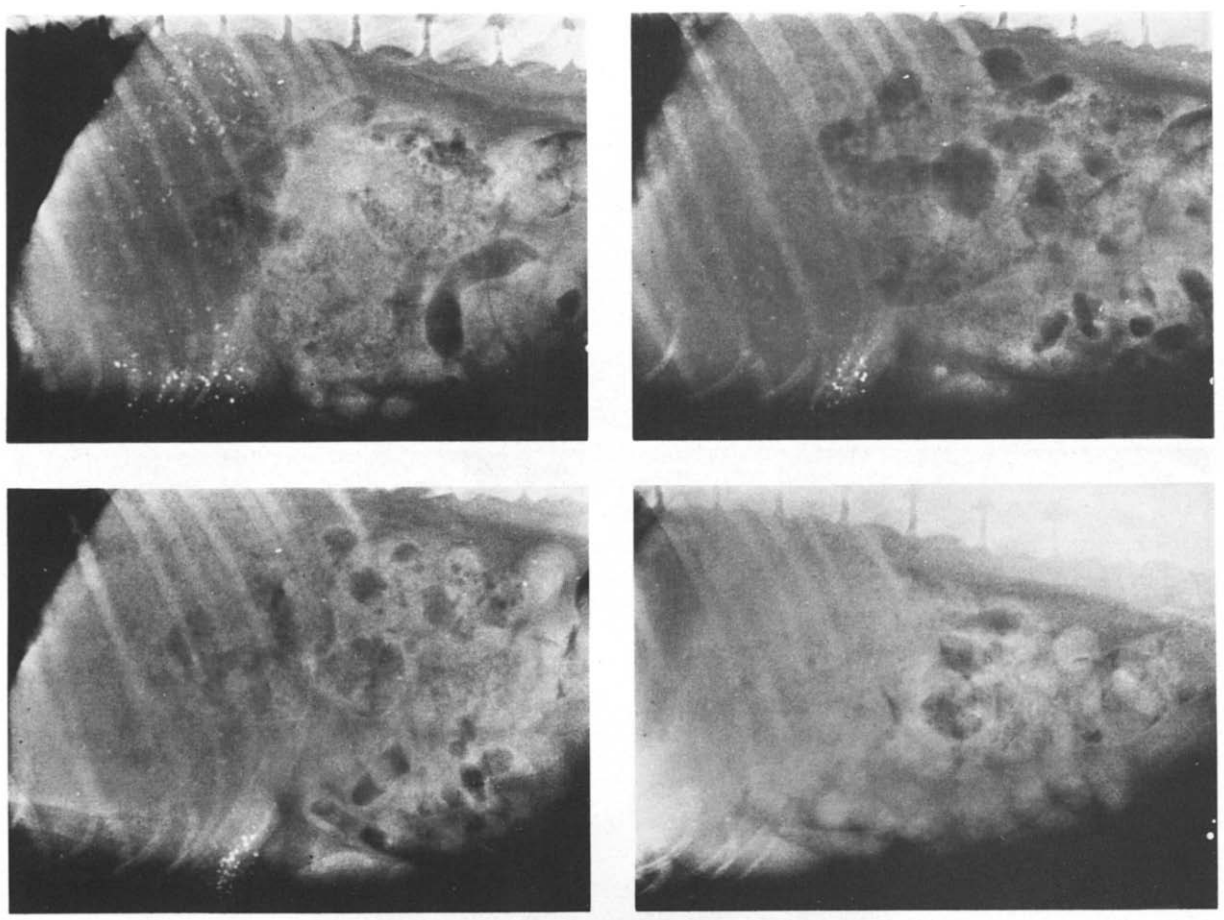

Fig. 7. X-rays showing the behaviour of HPMCP-coated (7%) granules in the stomach of a healthy dog at 0.25, 1, 1.5 and 5.5 h.

supported by Meyer et al. (1977), who reported that nearly all (97%) of the particles recovered from the duodenum of the dog had a diameter of 0.5 mm or less. It can thus be concluded that even smaller granules than the present ones would be needed in order to optimize the gastric emptying of multiple-unit preparations in pancreatic therapy. However, such arrangements are likely to aggravate existing problems in manufacture associated with the granulation and coating of particles.

No significant differences were observed in the gastric emptying times of granules given during the main meal (Fig. 1) or before (Fig. 7). It is obvious that in the latter case the granules, pre-administered with a small portion of food, switched the stomach from the prevailing fasting mode to the fed mode. The prolonged fed-state motility in the stomach resulted in delayed gastric emptying through the pylorus.

As seen on Figs. 3 and 5, CAP-coated granules showed no evidence of disintegration during a prolonged delay in the stomach. These preparations travelled to the lower part of the intestine and did not disintegrate until they had reached large intestine. In contrast, granules coated with HPMCP totally disappeared in the distal part of the small intestine (Fig. 1). It is evident that after passing through the pylours the HPMCP granules rapidly disintegrated in the upper part of the duodenum. On the other hand, part of the HPMCP granules may already have disintegrated in the stomach in front of the pylorus, as indicated by the clear reduction in the number of granules in

the vicinity of the pylorus during the fed state (Fig. 1).

In our previous study (Marvola et al., 1986) HPMCP-coated capsules were found to disintegrate in the vicinity of the pylorus, indicating that the pH in that area is around 5. Pancreatic enzymes released in powder form just in front of the pylorus would therefore be expected to remain stable and to pass through the pylorus simultaneously with food. The granules coated with 7% HPMCP showed an almost ideal disintegration for this purpose (Fig. 7). Following accumulation in the vicinity of the pylorus, disintegration of this preparation occurred over a period of 1–2 h. However, an even slower drug release should be aimed at since the gastric emptying of food generally takes longer. According to the literature, food is normally emptied from the stomach of the dog over a period of 1–4 h (Hinder and Kelly, 1977), and in some cases even after 4–5 h (Russell and Bass, 1985). Modifying the coating composition or the disintegrant in the core should make it possible to enhance the controlled release properties of this type of granule.

In summary, it can be concluded that pancreatic enzyme therapy using conventional enteric granules is unsatisfactory, similarly to the use of enteric-coated tablets, due to the prolonged gastric emptying time of these preparations. Future attempts should therefore focus on the development of special controlled-release preparations. Controlled drug release from granules in front of the pylorus could be achieved with HPMCP if the granules also contained a suitable disintegrant. Optimum coatings would be those in which the amount of HPMCP varied between 20 and 30% of the total weight of the granules.

References

Fara, J.W., Physiological limitations: gastric emptying and transit of dosage forms. In L.F. Prescott and W.S. Nimmo (Ed.), *Rate Control in Drug Therapy*, Churchill Livingstone, Edinburgh, 1985, pp. 144–150.

Graham, D., Enzyme replacement therapy of exocrine pancreatic insufficiency in man: relation between in vitro enzyme activities and in vivo potency in commercial pancreatic extracts. *New Engl. J. Med.*, 296 (1977) 1314–1317.

Hinder, R.A. and Kelly, K.A., Canine gastric emptying of solids and liquids. *Am. J. Physiol.*, 133 (1977) 335–340.

Ihse, I., Lilja, P. and Lundquist, I., Intestinal concentrations of pancreatic enzymes following pancreatic replacement therapy. *Scand. J. Gastroenterol.*, 15 (1980) 137–144.

Itoh, T., Higuchi, T., Gardner, C. and Caldwell, L., Effect of particle size and food on gastric emptying time of non-disintegrating solids in beagle dogs. *J. Pharm. Pharmacol.*, 38 (1986) 801–806.

Marvola, M., Heinämäki, J., Happonen, I. and Westermarck, E., The fate of single-unit enteric-coated drug products in the stomach of the dog. *Acta Pharm. Fenn.*, 95 (1986) 59–70.

Meyer, J.H., Mandiola, S., Shadchehr, A., Cohen, M., Dispersion of solid food by the canine stomach. *Gastroenterology*, 72 (1977) 1102.

Meyer, J.H., Thomson, J.B., Cohen, M.B., Shadchehr, A. and Mandiola, S., Sieving of solid food by the canine stomach and sieving after gastric surgery. *Gastroenterology*, 76 (1979) 804–813.

O'Reilly, S., Wilson, C.G. and Hardy, J.G., The influence of food on the gastric emptying of multiparticulate dosage forms. *Int. J. Pharm.*, 34 (1987) 213–216.

Russell, J. and Bass, P., Canine gastric emptying of polycarbophil: an indigestible, particulate substance. *Gastroenterology*, 89 (1985) 307–312.

Wagner, J.G., Veldkamp, W. and Long, S., Enteric coating IV. In vivo testing of granules and tablets coated with styrene–maleic acid copolymers. *J. Am. Pharm. Assoc., Sci. Ed.*, 49 (1960) 128–132.