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Formulations releasing the drug proximal to the pylorus in the dog

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Summary

To overcome various difficulties associated with the replacement of drug therapy for pancreatic insufficiency, film-coated tablets releasing the drug in front of the pylorus were developed and studied in dogs using a series of X-rays. The tablets, containing pregelatinized starch or carmellose as a disintegrant, were coated with cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP) or methacrylic acid co-polymer (Eudragit L) combined with the soluble polymers, hydroxypropyl methylcellulose (HPMC) or methacrylate esters co-polymer (Eudragit E). Sustained-release tablets were coated with ethyl cellulose (EC) containing small amounts of HPMC.

When administered with food, controlled drug release was achieved in front of the pylorus with conventional enteric materials if the tablets also contained a suitable disintegrant. EC–HPMC-coated tablets act as a prolonged action formulation, releasing the drug for up to 5–7 h in front of the pylorus and thereafter in the intestine. As demonstrated in these dog studies, it should therefore be possible to develop sustained-release formulations which release pancreatic enzymes for a prolonged period of time in a site favourable for their digestive function.

Introduction

Malabsorption secondary to exocrine pancreatic insufficiency has for years been, and still is, most commonly treated with enteric-coated tablets containing acid-labile pancreatic enzymes. However, due to the several physiological factors affecting the bioavailability of single-unit enteric preparations, the clinical response has been unsatisfactory. The physiological limitations shown to be responsible for the low potency of these supplements include prolonged gastric emptying, hyposecretion of gastric acid, reduced pancreatic-bicarbonate secretion into the intestine, and altered bile salt kinetics (Perry and Gallagher, 1985).

Problems associated with gastric emptying and the disintegration of single-unit enteric preparations have prompted the development of new ways of administering exogenous pancreatic enzymes. The use of several oral antacids and H_2-receptor antagonists as adjunctive therapy for oral enzyme replacement has been introduced to prevent gastric inactivation of uncoated exogenous pancreatic enzymes (Perry and Gallagher, 1985). The in vivo behaviour and clinical effectiveness of enteric-coated encapsulated microspheres and enteric-

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coated granules as enzyme supplements have been examined at length, with varying success (Graham, 1979; Dutta et al., 1983; Petersen et al., 1987; Heinämäki et al., 1988). However, despite appreciable progress achieved in the drug therapy of maldigestion, an ideal treatment for pancreatic insufficiency has yet to be devised.

Our previous study with dogs showed that non-disintegrating tablets given with food accumulated in the antrum within roughly 1 h, remaining there for 6–8 hours (Marvola et al., 1986). The pH in the vicinity of the pylorus was found to be about 5, and since pancreatic enzymes are irreversibly inactivated at a pH of less than 4.5 (Heizer et al., 1965), this area is optimal for enzyme function. Consequently, and for the reasons mentioned above, it would seem more reasonable to aim for the vicinity of the pylorus rather than, classically, the intestine.

The aim of the present study was to investigate the possibility of developing: (1) a controlled-release tablet releasing the drug in front of the pylorus 1–3 h after administration; and (2) a single-unit sustained-release tablet releasing the drug continuously in the vicinity of the pylorus. Drug release from the formulations was controlled using soluble polymers (hydroxypropyl methylcellulose or methacrylate esters co-polymer) in 3 different enteric coatings (cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate or methacrylic acid co-polymer) on tablets containing either pregelatinized starch or carmellose as a disintegrant. Sustained-release tablets were coated with ethyl cellulose containing small amounts of hydroxypropyl methylcellulose.

Materials and Methods

Preparation of core tablets

The following materials were used for core tablet preparation: barium sulphate (Barisulf-HD, Leiras), caffeine (Ph.Eur.), pregelatinized starch (Starch 1500, Colorcon), carmellose (Hercules), potato starch (Ph.Eur.), microcrystalline cellulose (Avicel PH 102, FMC), lactose (Ph.Eur.), talc (Ph.Eur.), magnesium stearate (Ph.Eur.) and gelatin (Ph.Eur.).

TABLE 1

Composition of barium sulphate (I–VI) and caffeine (VII) core tablets

Ingredient	Formulation				
	I–II	III–IV	V	VI	VII
Barium sulphate	25%	25%	24%	25%	–
Caffeine	–	–	–	–	24%
Pregelatinized starch/ Carmellose	10%	20%	–	–	–
Microcrystalline cellulose	–	–	25%	–	–
Lactose	– *	– *	– *	75%	72%
Talc	–	–	–	–	3%
Magnesium stearate	–	–	1%	–	1%
Basic granules for tabletting (0.4–1.0 mm)	65%	55%	50%	–	–

* Lactose included in the composition of basic granules.

The composition of the core tablets is shown in Table 1. In formulations I–V the basic granules were prepared according to the Nordic Pharmacopoeia (Granulatum simplex) containing 30% lactose, 69% potato starch and 1% gelatin. Formulations VI and VII were prepared by wet granulation with 4% gelatin solution.

The core tablets were compressed in a Korsch EK-O single-punch machine using biconvex 5 mm, 9 mm and capsule-shaped punches. The tablets weighed 90 ± 2 mg (formulations I–VII; 5 mm), 344 ± 12 mg (V; 9 mm) and 863 ± 10 mg (V; capsule-shaped). The tablet strength was set to 50–60 N (Schleuniger 2-E/205).

Coating

The coating materials studied were: methacrylic acid co-polymer (Eudragit L, Röhm Pharma); methacrylate esters co-polymer (Eudragit E, Röhm Pharma); cellulose acetate phthalate (CAP) (Eastman Kodak); hydroxypropyl methylcellulose (HPMC) (Dow Chemical Co.); hydroxypropyl methylcellulose phthalate (HPMCP) (HP-50, Shin-Etsu Chemical) and ethyl cellulose (ECN-10) (Hercules). Isopropanol (E. Merck), ethanol (Alko), dichloromethane (E. Merck) and purified water were used as solvents, and dibutylsebacinate (Fluka AG) or glycerol (Ph.Eur.) were added as plasticizers.

Four coating solutions were prepared as follows:

(1) Eudragit L-Eudragit E 95:5	
Methacrylic acid co-polymer, Eudragit L	12.3%
Methacrylate esters co-polymer, Eudragit E	0.7%
Isopropanol	84.0%
Purified water (formulations I–IV)	3.0%
(2) CAP-HPMC 45:55	
CAP	3.2%
HPMC	3.9%
Dichloromethane	61.0%
Ethanol	30.5%
Dibutylsebacinate (formulation V)	1.4%
(3) HPMCP (HP-50)	
HPMCP (HP-50)	10.0%
Dichloromethane	45.0%
Ethanol (formulation V)	45.0%
(4) EC-HPMC 75:25	
Ethyl cellulose	3.7%
HPMC	1.3%
Glycerol	1.0%
Ethanol	31.3%
Dichloromethane (formulations VI–VII)	62.7%

The coatings were applied using a fluidized bed coating technique (Aeromatic Strea 1, Aeromatic AG). The first batch (formulation I) consisted of 55 g of tablets and subsequent batches of 200 g. The inlet air temperature was adjusted to $30 \pm 1°C$ ($38 \pm 1°C$ for HPMCP solution) and the outlet air temperature to $26 \pm 1°C$ ($29 \pm 1°C$). The pneumatic spraying pressure was kept at 1.0 bar. The air flow rate was 110 $m^3 \cdot h^{-1}$.

The theoretical amounts of coating were 3 mg/cm^2 for EC-HPMC tablets; 3, 5 and 10 mg/cm^2 for Eudragit L–Eudragit E tablets; 10 mg/cm^2 for CAP-HPMC tablets and 20 mg/cm^2 for HPMCP tablets.

Disintegration tests

Disintegration tests were carried out with the Ph.Eur. basket rack assembly apparatus (Sotax DT3, Sotax AG). Phosphate–citrate buffer solutions at pH 2.2 and 5.0 were used as the disintegration medium at 37 °C. The disintegration times were evaluated as: (1) time to rupture of the coat; and (2) time to complete disintegration of the barium sulphate tablet.

Dissolution control test

Adequate coating was ensured by in vitro evaluation of 6 sustained-release caffeine tablets analogous to formulation VI using the USP XX paddle method. The dissolution medium was 800 ml phosphate–citrate buffer at pH 2.2 and 37 °C. The stirring rate was adjusted to 50 min^{-1}.

Experiment with dogs

Three adult beagle dogs were fasted overnight for at least 10 h. A standard semisolid meal of commercial food was given the following morning, the drug products being mixed into this. No additional food was given during the study 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 and 7 h. The accuracy of the timing was ± 5 min; larger deviations are mentioned separately.

Results

In vitro

Table 2 shows the results of the disintegration test with Eudragit L–Eudragit E-coated barium sulphate tablets incorporating either pregelatinized starch (Starch 1500) or carmellose as an extragranular disintegrant in the core. The data given are ranges of the disintegration times of 6 tablets evaluated at pH 2.2 and pH 5.0. The disintegration times of CAP–HPMC- and HPMCP-coated tablet cores were 201–228 min at pH 2.2 and 27–31 min at pH 5.0, respectively.

In up to 80% of the sustained-release tablets caffeine release followed zero-order kinetics fairly well, with a lag time of 48 min (Fig. 1), according to the linear equation: $y = 0.203x - 9.800$ ($r = 0.998$).

TABLE 2

Disintegration times of tablets with different Eudragit L–Eudragit E coats in phosphate-citrate buffer solutions at pH 2.2 and 5.0 (n = 6)

Coat	Disintegrant	Disintegration time (min)			
		pH 2.2		pH 5.0	
		Coat	Core	Coat	Core
Eudragit L + E (95 : 5) 3 mg/cm	Starch 1500 20%	13–23	17–26	14–18	16–23
	Carmellose 10%	6–14	9–18	4–12	27–48
	Carmellose 20%	11–13	20–35	10–12	66–110
Eudragit L + E (95 : 5) 5 mg/cm	Starch 1500 10%	22–45	28–55	15–40	19–45
	Starch 1500 20%	22–42	35–50	25–47	30–56
	Carmellose 10%	12–17	15–23	18–22	30–53
	Carmellose 20%	14–27	20–34	15–32	75–120
Eudragit L + E (95 : 5) 10 mg/cm	Starch 1500 10%	24–35	41–120	20–35	26–87
	Starch 1500 20%	36–50	46–67	36–59	40–65

In vivo

Fig. 2 illustrates the gastric behaviour of Eudragit L–Eudragit E-coated (95 : 5) tablets containing pregelatinized starch (10%) as an extragranular disintegrant in the core. Following fairly prolonged accumulation in front of the pylorus (1–1.5 h), most tablets (6 out of 9) disintegrated readily in its vicinity. Three tablets, however, were retained randomly in the body and antrum, remaining there intact for another hour. Rapid disintegration eventually occurred in the vicinity of the pylorus 2.5–3.5 h after administration. Despite partial deformation of the tablets during transit, none disintegrated until they reached the pylorus. Modifying the coat thickness (3 mg/cm^2 and 5 mg/cm^2) produced no significant differences in disintegration times in vivo.

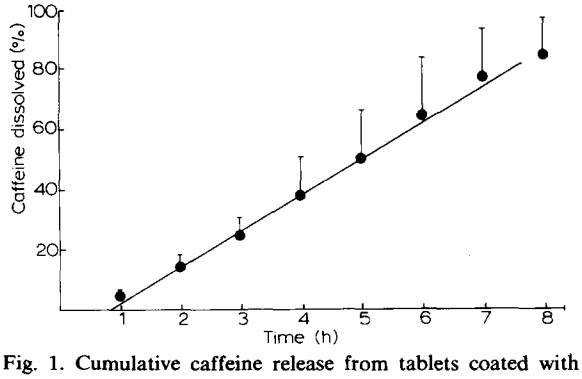

Fig. 1. Cumulative caffeine release from tablets coated with EC–HPMC (75 : 25) plasticized with glycerol. Each point represents the mean ± S.D. (n = 5).

The gastric behaviour of Eudragit L–Eudragit E tablets incorporating 10% of carmellose as a disintegrant in the core is shown in Fig. 3. As in the previous test, most of the tablets ingested (12/15) were found in the distal regions of the stomach within 1.5 h. During this time the first signs of partial tablet deformation were observed, being predominant at 2 h. Nevertheless the tablets failed to disintegrate in the vicinity of the pylorus. Finally, at 5 h the tablets were swept into the duodenum and partially disintegrated in the proximal part of the intestine.

To eliminate the effects of possible-inter-individual variations on disintegration times in vivo, the following study was carried out in the same subject using 3 barium sulphate tablets with a different coat and shape (Fig. 4). The coating materials examined were Eudragit L–Eudragit E (95 : 5), CAP–HPMC (45 : 55) and HPMCP (HP-50), and the disintegrant agent used in the first core was pregelatinized starch (Starch 1500). X-rays of the stomach clearly showed the Eudragit tablets to have disintegrated close to the pylorus within 1–2 h. Disintegration of the other tablets occurred at 2–3 h, also in the vicinity of the pylorus. The active ingredients were found to pass through the pylorus only if in fine powder form, showing the tremendous selectiveness of this anatomical sphincter during the digestive mode.

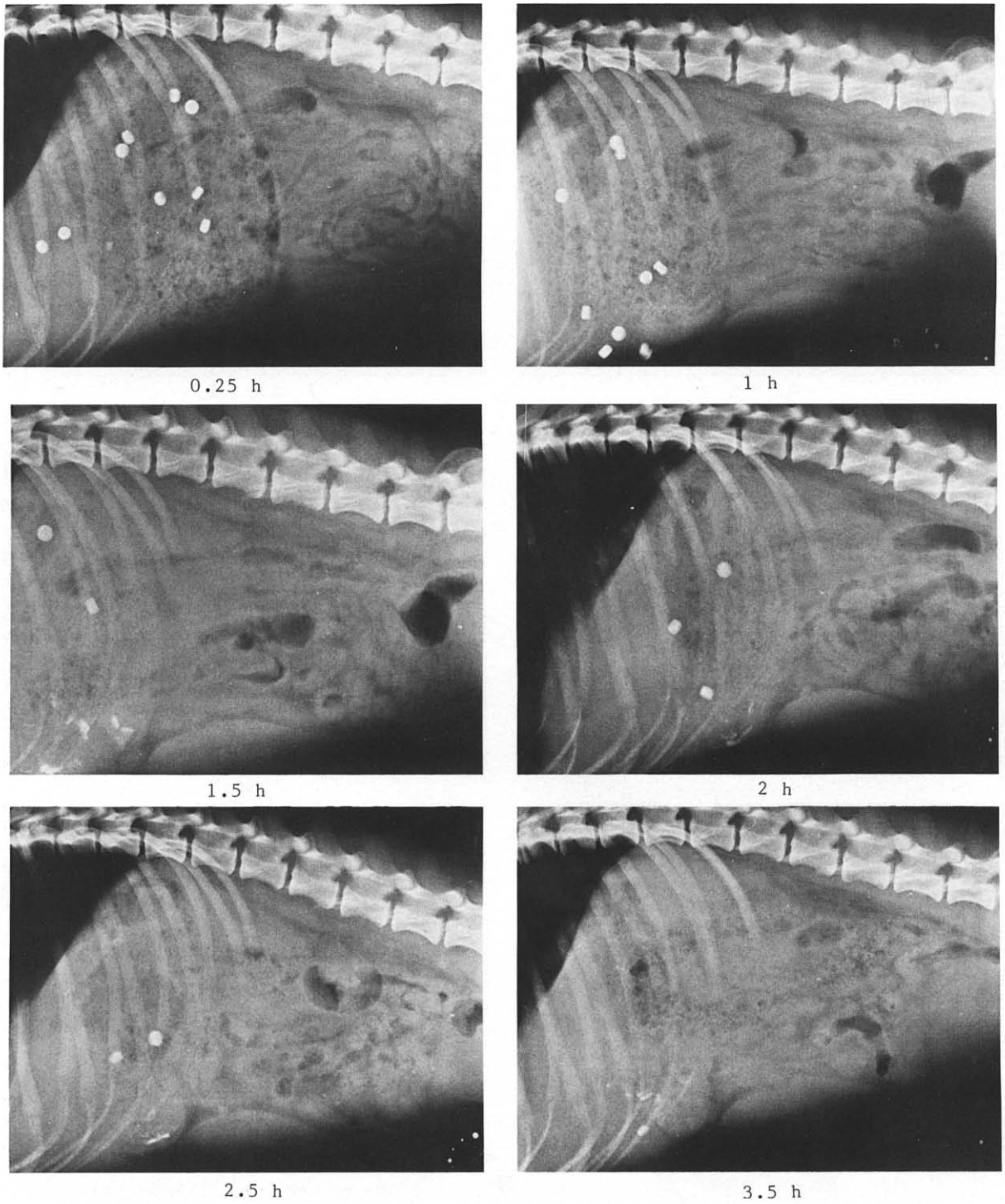

Fig. 2. X-Rays showing the behaviour of Eudragit L–Eudragit E-coated tablets (95 : 5; 10 mg/cm^2) with pregelatinized starch as a disintegrant (10%) in the core in the stomach of the dog.

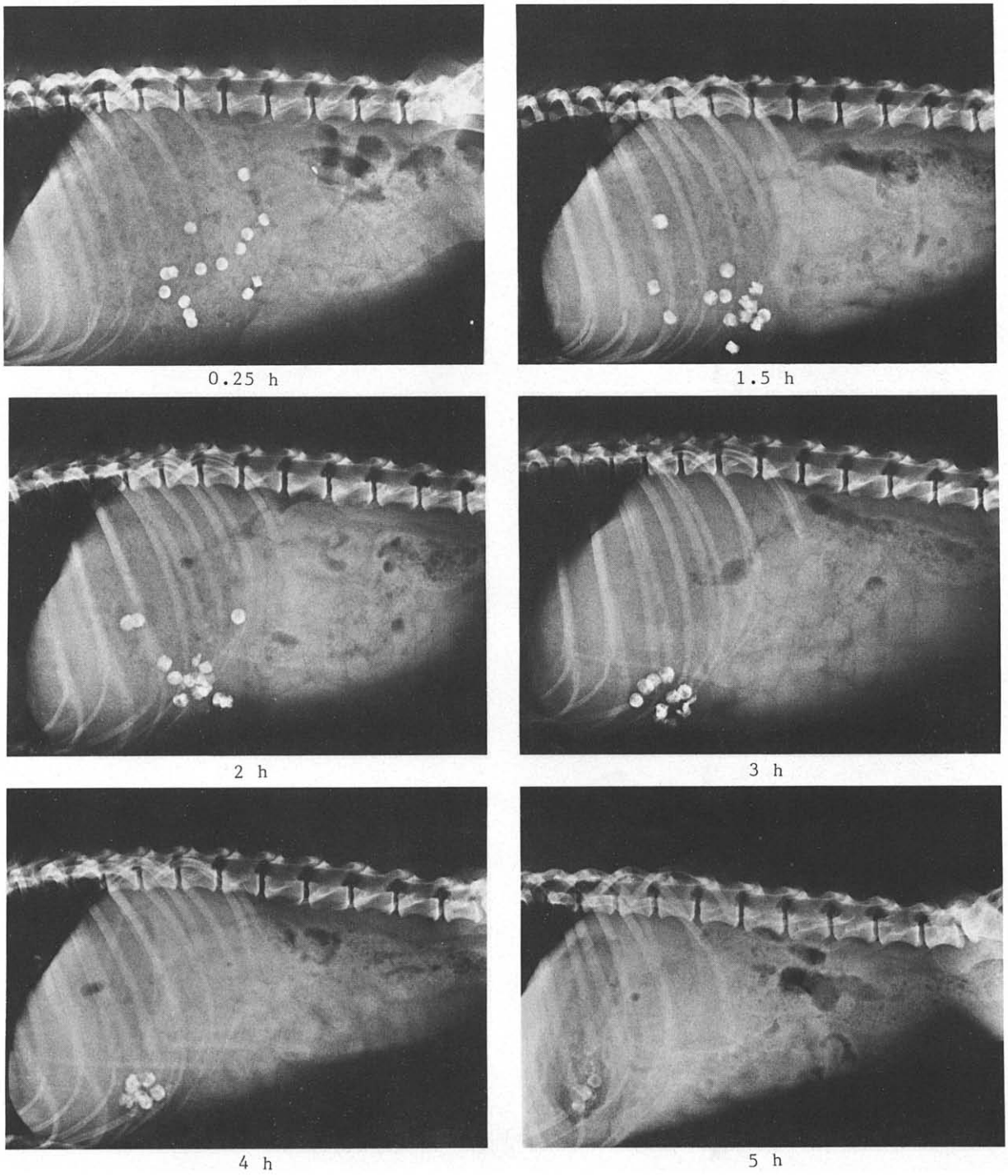

Fig. 3. X-Rays showing the behaviour of Eudragit L–Eudragit E-coated tablets (95 : 5; 5 mg/cm^2) with carmellose as a disintegrant (10%) in the core in the stomach of the dog.

Finally, the behaviour of sustained-release EC–HPMC tablets was followed throughout the GI tract (Fig. 5). These tablets, showing no signs of adhesion to the gastric mucosa in the distal part of the stomach, were clustered in front of the pylorus at 1 h. At 4–5 h the tablets (6) appeared

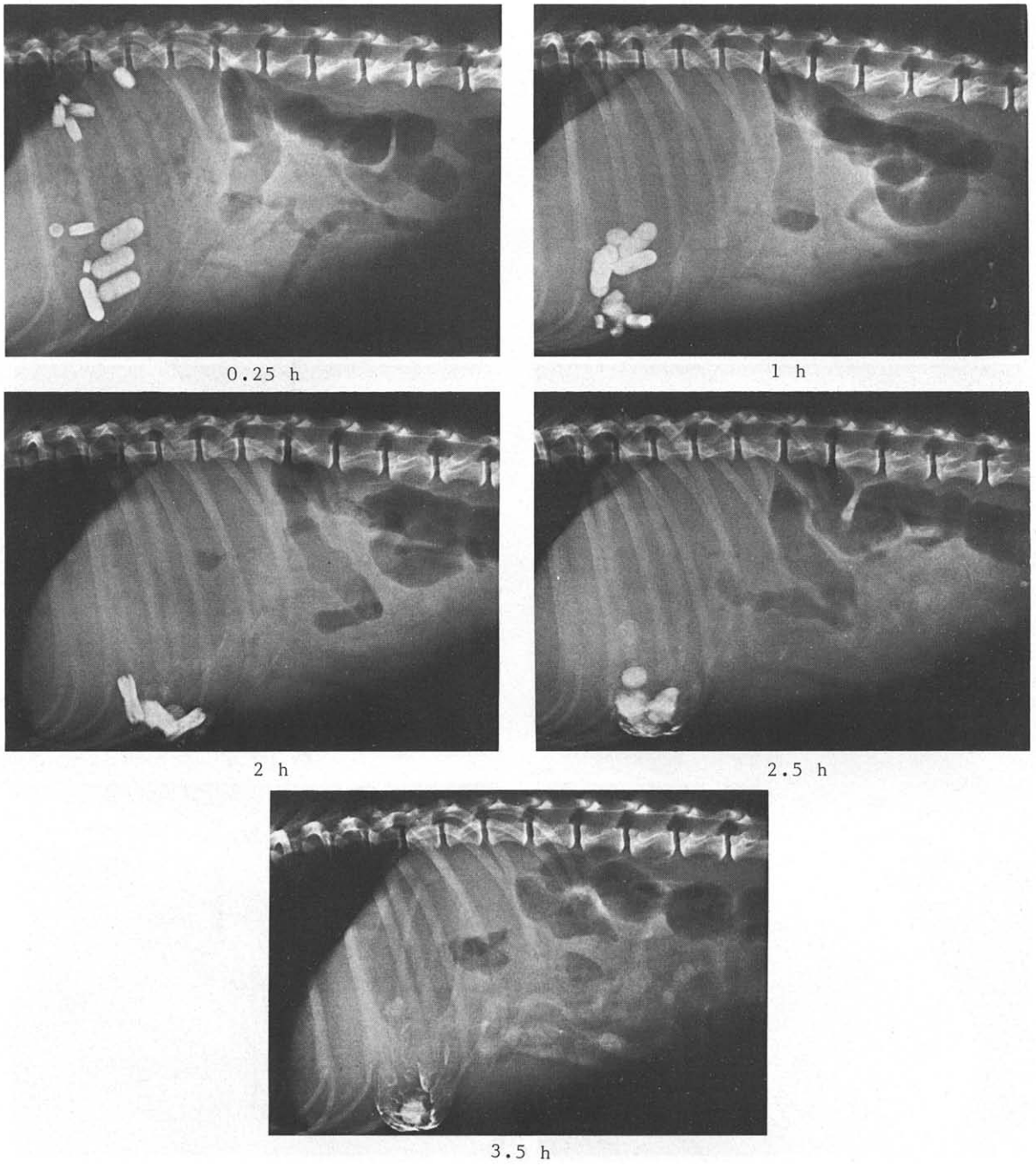

Fig. 4. X-Rays showing the behaviour of different coated tablets containing pregelatinized starch as a disintegrant (10%) in the core in the stomach of the dog. Coats: ○, Eudragit L–Eudragit E (95 : 5); ○, CAP–HPMC (45 : 55); ⬭, HPMCP (HP-50).

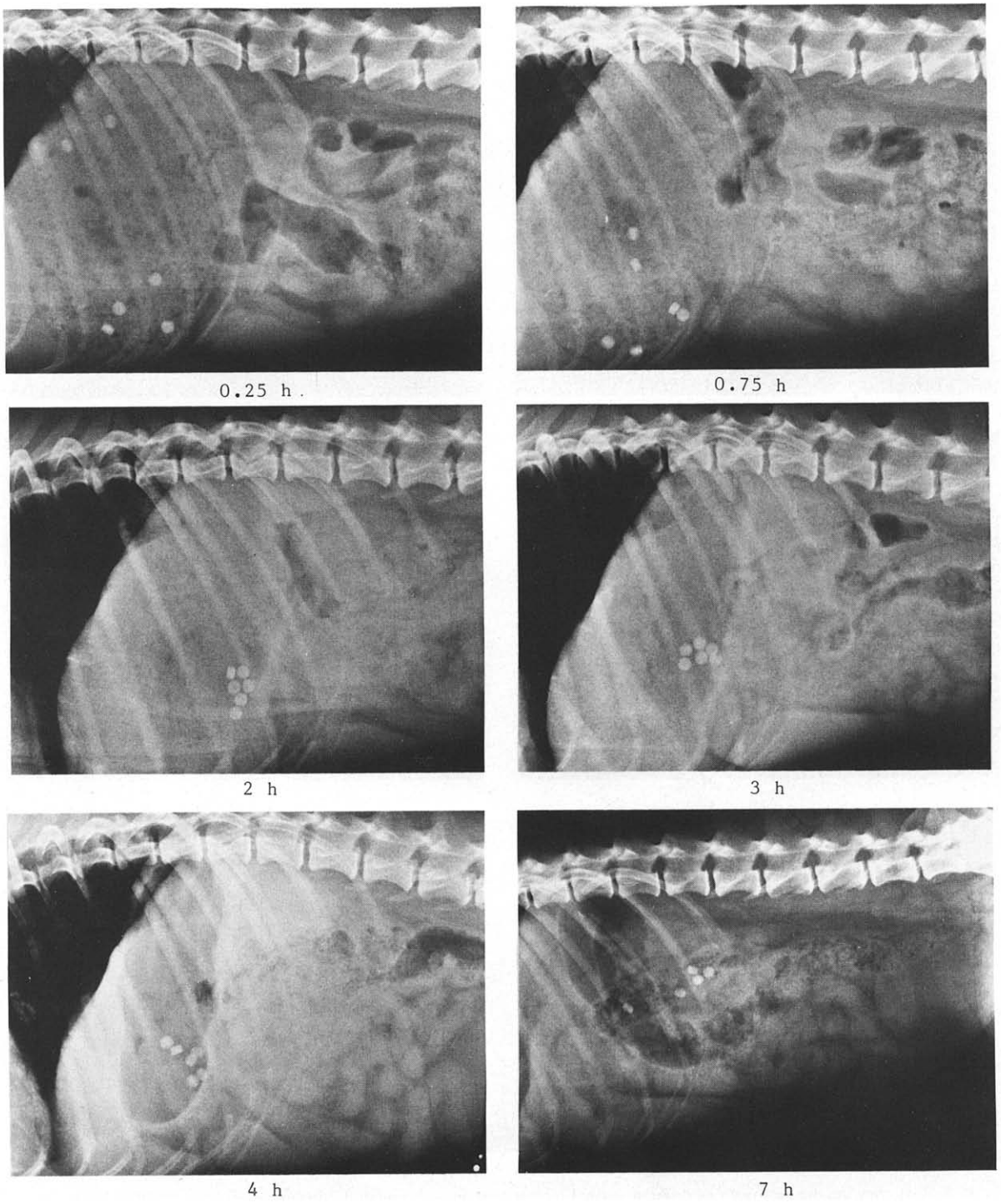

Fig. 5. X-Rays showing the behaviour of sustained-release EC–HPMC-coated tablets (75 : 25; 3 mg/cm^2) in the stomach of the dog.

intact and sharply outlined in the vicinity of the pylorus. At the end of the digestive mode the tablets were swept into the small intestine by the "housekeeper" wave, moving closely together along the intestine. Finally, at 7 h 5 of the 6 tablets, now partially deformed, were seen in the lower ileum.

Discussion

For formulations releasing the drug in front of the pylorus, the duration of gastric transit plays a major role in determining the onset of action, and consequently, the potency of the product. In the present study faster and more uniform accumulation in front of the pylorus was obtained with large model tablets (Fig. 4) than with smaller ones 5 mm in diameter (Figs. 2 and 5). Small tablets, when randomly scattered throughout the upper part of the stomach, moved particularly slowly from the fundus and body down to the antrum, significantly delaying the onset drug release in front of the pylorus. Obviously, the main reason behind such random "trapping" in the upper parts of the stomach is local differences in motor activity during the digestive mode, reported to be rather mild in the upper part of the stomach but frequent and vigorous in the antrum (Strombeck, 1979). Therefore, especially when formulating sustained-release products, careful attention should be paid to sufficient size, otherwise large amounts of drug will be prematurely released in the gastric regions, severely affecting drug action. The shape of the model tablets was found to have no significant influence on their accumulation in front of the pylorus.

With few exceptions, controlled drug release in front of the pylorus started 1–3.5 h after ingestion. This closely correlates with the gastric emptying time of food, reported to be 1–4 h in the dog (Hinder and Kelly, 1977). It is therefore evident that pancreatic enzymes, if released close to the pylorus during the digestive mode, will be effectively transfered into the proximal duodenum, where significant absorption of food takes place. Since the release occurs proximally to the GI tract, the length of small intestine available to enzymatic digestion and absorption will be greater than with e.g. enteric-coated preparations. As shown in our previous studies with enteric-coated single- and multiple-unit preparations, the main reason for failure to accomplish the goals discussed above is the prolonged gastric residence of dosage forms administered with food (Marvola et al., 1986; Heinämäki et al., 1988).

The present results show that controlled drug release can be achieved in front of the pylorus with conventional enteric polymers if the tablets also contain a permeability-increasing agent and a suitable disintegrant. Tablets coated with Eudragit L–Eudragit E (95 : 5) and containing pregelatinized starch (10%) provided highly reliable and rapid drug release in the vicinity of the pylorus 1 h after administration (Fig. 2). Partial deformation of the tablets just before disintegration was due to the controlled increase in permeability of the coat to water in the acidic environment (Eudragit E-component). The penetration of water into the tablet core caused rapid swelling of the pregelatinized starch, accelerating final disintegration in front of the pylorus. The extragranular position of the starch was found to be highly favourable for this occurrence, confirming earlier findings with starch derivatives (Shotton and Leonard, 1976) showing in vitro disintegration to be more rapid with extragranular than intragranular preparations. The optimum extragranular concentration of pregelatinized starch was found in this study to be 10%, disintegration times remaining clearly stable above this value (Table 2).

The disintegrant efficiency of extragranular carmellose in Eudragit L-Eudragit E-coated (95 : 5) tablet cores was found to be particularly poor in the dog stomach. As seen in Fig. 3, coated tablets containing 10% of carmellose failed to disintegrate in the vicinity of the pylorus during the digestive mode over a period of 4 h. So far only in vitro results have been reported, showing poorer disintegration properties of carmellose and other adhesive disintegrants when used in high concentrations in the tablet cores (Khan and Rhodes, 1973, 1975; Gissinger and Stamm, 1980). According to these reports, the main reason for the low potency

of the disintegrant was viscous gel formation in the tablets containing more than 10% carmellose when in contact with water. This corroborates our own results in vitro that show more rapid disintegration of tablets with 10% carmellose than those with 20% (Table 2). The present in vivo results clearly suggest, however, that gel formation with carmellose is deleterious to tablet disintegration, even at a concentration of 10%. Obviously, the high pH in front of the pylorus, derived from the minor reflux of intestinal contents into the stomach (Sonnenberg et al., 1982), partly facilitates hydration of the carmellose, hindering tablet disintegration. This proposition is supported by the prolonged disintegration times of the products in vitro at pH 5 (Table 2).

The correlation between in vivo and in vitro disintegration times was relatively poor: (1) coat thickness affected disintegration in vitro but not in vivo; and (2) the disintegrant had a minimal effect on disintegration time in vitro but a clear effect in vivo (carmellose). Since, with few exceptions, the disintegration times in vitro at pH 2.2 were considerably shorter than those obtained in vivo and at pH 5.0, even higher pH should be used in vitro to better mimic conditions in the dog stomach during the digestive mode. On the other hand, the poor correlation might partly result from the low volumes of gastric fluids in the dog stomach, difficult to consider in in vitro evaluations.

Controlled drug release was achieved in front of the pylorus with a low pH-sensitive enteric material (HPMCP; HP-50) when the tablets were co-administered with food. According to Nishimura et al. (1984), rapid disintegration of HPMCP (HP-50)-coated tablets occurred in the proximal duodenum of the dog when these were administered to the empty stomach. It is therefore evident that the behaviour of HPMCP (HP-50)-coated tablets in the GI tract is highly dependent on the timing of drug administration in relation to food; on co-administration with food drug release can, due to prolonged retention of the tablets in the stomach, be targeted to the front of the pylorus, avoiding drug release in the intestinal tract. In the case of pancreatic enzymes, drug release from HPMCP (HP-50)-coated tablets will always occur in the regions most favourable for pancreatic enzyme function, since the dissolution pH of HPMCP (HP-50), pH 5, is slightly above the critical pH for the inactivation of pancreatic enzymes. According to the literature, pancreatic enzymes, especially lipase, are irreversibly inactivated by gastric acid and pepsin at a pH below 4.5 (Heizer et al., 1965).

Their sufficient solubility in water and body fluids makes it theoretically possible for pancreatic enzymes to be formulated in sustained-release dosage form, with continuous drug release based on the semi-permeable membrane. The present results show that such a formulation, once we succeed in designing it, will offer certain advantages over the former replacement therapy. (1) Pancreatic enzymes, given as sustained-release EC–HPMC (75 : 25)-coated tablets, can be reliably targetted to the front of the pylorus, since there is apparently no adhesion to the gastric mucosa or premature gastric emptying during the digestive mode. (2) Contrary to single-unit enteric preparations, the potency of these products is not reduced by slower gastric emptying during the digestive mode, making it possible to administer them simultaneously with food. (3) Slow release of the drug through the semi-permeable membrane (EC-HPMC) in the vicinity of the pylorus will provide a therapeutic response over a prolonged period of time. However, one should aim for more rapid drug release than 8 h (Fig. 1), since gastric emptying in dogs generally takes only 1–4 h. According to the literature, this can be reliably achieved by increasing the amount of HPMC up to 40% in the EC–HPMC coat composition (Kannikoski, 1984).

However, before further studies with sustained-release pancreatic enzyme formulations can be arranged, more information is required concerning the external factors that influence the gastric residence time of single-unit products. Only then can we predict more reliably the behaviour of sustained-release tablets in the GI tract of the dog. For instance, the influence of such factors as the quantity and quality of food, quantity of water and the timing of food and water intake in relation to drug administration on gastric emptying of the tablets should be studied in greater detail.

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