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Disintegration of hard gelatin capsule formulations in the dog stomach — a radiological study

Martti Marvola[1,2], Ann-Mari Hannula [1], Elias Westermarck [3], Irmeli Happonen [3] and Tarja Kopra [2]

[1] *University Pharmacy, University of Helsinki, Helsinki (Finland),* [2] *School of Pharmacy, University of Helsinki, Helsinki (Finland) and* [3] *Department of Clinical Veterinary Medicine, College of Veterinary Medicine, Helsinki (Finland)*

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Summary

The final decision as to the suitable composition of an oral drug formulation should be made on the basis of in vivo studies. A radiological technique was developed for studying the in vivo disintegration of hard gelatin capsules in the stomach of the dog. Highly water-soluble additives such as sucrose and lactose caused rapid disintegration (10–15 min). Formulations containing semisolid material disintegrated in roughly 20 min. The mean disintegration time for capsules containing microcrystalline cellulose or dicalcium phosphate dihydrate was 37 min and 44 min, respectively. Capsules containing corn starch or carboxymethylcellulose sodium disintegrated very slowly and clearly adhered to the gastric mucosa. Very rapid disintegration (mean 9 min) was observed with capsules containing small coated pellets, which indicates that hard gelatin capsules may be a good dosage form for multiparticular modified-release formulations. The correlation between in vitro and in vivo data was unsatisfactory.

Introduction

As is obvious from the large number of publications, the in vitro disintegration of hard gelatin capsules is a popular subject of study. However, the final decision concerning the suitable composition of a capsule formulation should be made on the basis of in vivo experiments.

In man, the in vivo disintegration of hard gelatin capsules is generally studied by external scintigraphic monitoring of gamma emitting isotope formulations (Casey et al., 1976; Alpsten et al., 1979; Hunter et al., 1980). The disintegration of sodium bicarbonate capsules can also be evaluated by measuring the change in pH of the gastric juice (Eckert, 1967). A third possibility is radiology. As early as 1958 Wagner suggested that x-ray monitoring of the in vivo disintegration of enteric-coated tablets in dogs would be a useful method of screening new enteric coatings (Wagner et al., 1958). Our own experience confirms that the disintegration of both tablets and capsules in the stomach of the dog can be detected by x-rays (Marvola et al., 1986).

In previous studies considerable variation in the in vivo disintegration times of capsules – from

Correspondence: M. Marvola, University Pharmacy, University of Helsinki, SF-00510 Helsinki, Finland.

a few minutes to roughly one hour — has been observed. The water solubility of the capsule content has been shown to correlate with the disintegration time; capsules with water-soluble contents have been found to disintegrate faster than those with water-insoluble contents (Eckert, 1967; Casey et al., 1976; Alpsten et al., 1979; Hunter et al., 1980; Hunter et al., 1982). Adherence of the capsules to the gastric mucosa has also been reported (Hunter et al., 1980; Hunter et al., 1982).

No systematic investigations exist concerning the possible role of pharmaceutical additives in the in vivo disintegration of capsule formulations or in their adherence to the gastrointestinal mucosa. One reason may be that all in vivo experiments in man are inconvenient and have a number of limitations and drawbacks (Fell and Digenis, 1984).

The aim of the present study was: (1) to develop an x-ray method by which the disintegration of different capsule formulations in the stomach of the dog could be studied simultaneously, and (2) to study the effect of common additives on the disintegration of hard gelatin capsule formulations in vivo.

Materials and Methods

Substances

The substances used in the experiments were as follows: barium sulphate (Ph. Eur.), sucrose (Tabfine S 100-I, Finnish Sugar Co., Ltd.), lactose (Ph. Eur., De Melkindustrie Veghel), microcrystalline cellulose (Emcocel, Edward Mendell Ltd.), dicalcium phosphate dihydrate (Emcompress, Edward Mendell Ltd.), corn starch (maydis amylum, Ph. Eur. Thibola DRM), carboxymethylcellulose sodium (USP XXI), polyethylene glycol 1500 (Macrogolum 1500, Ph. Eur.), peanut oil (arachidis oleum, Ph. Nord.), beeswax (cera alba, Ph. Eur.), ethylcellulose (Ethocel N-10, Hercules) and gelatin (Ph. Nord.)

Film-coated pellets

Lactose either alone or blended with barium sulphate (3 : 1) was moistened with a water solution of gelatin (10%) and passed manually through a 2 mm sieve. The dry granules (sieve fraction 0.7–1.7 mm) were coated with 5% ethylcellulose solution (solvent: ethanol/toluene 1 : 4) in a fluidized bed coater (Aeromatic Strea I, Aeromatic AG).

Capsule formulations

Size O hard gelatin capsules (Posilok, Elanco) were used in all formulations.

Each pharmaceutical additive in powder form was initially blended with barium sulphate (3 : 1) and passed through a 0.3 mm sieve to give a sufficient amount for a batch of 100 capsules (68 ml). The capsule shells were filled manually using a Feton apparatus.

Polyethylene glycol 1500 was melted over a water bath (50 °C) and barium sulphate (25%) added. Beeswax (37.5%) was melted over a water bath (45 °C) and peanut oil (37.5%) and barium sulphate (25%) were added. Capsule shells were filled with the liquid suspensions using disposable syringes.

Two types of capsule containing ethylcellulose-coated pellets were prepared; one containing barium pellets only, the other containing roughly 1/3 barium sulphate pellets and 2/3 lactose pellets.

To facilitate identification of the various formulations on the x-rays, small metal balls (diameter 3 mm), rings (diameter 4 mm) or rods (length 5 mm) were added to most of the formulations, as shown in the results.

Disintegration test

The in vitro disintegration tests were performed according to the European Pharmacopoeia (Sotax DT 3 apparatus, Sotax AG) using purified water or 0.1 M hydrochloric acid as a medium. Twelve capsules were tested from each formulation.

Experiments with dogs

Two healthy adult dogs were used in the experiments, one a female Finnish harrier and the other a female beagle. The dogs were fasted overnight for at least 12 h. A standard semisolid meal was prepared from commercial food pellets and the drugs added before feeding. No additional food or water was allowed during the experiments.

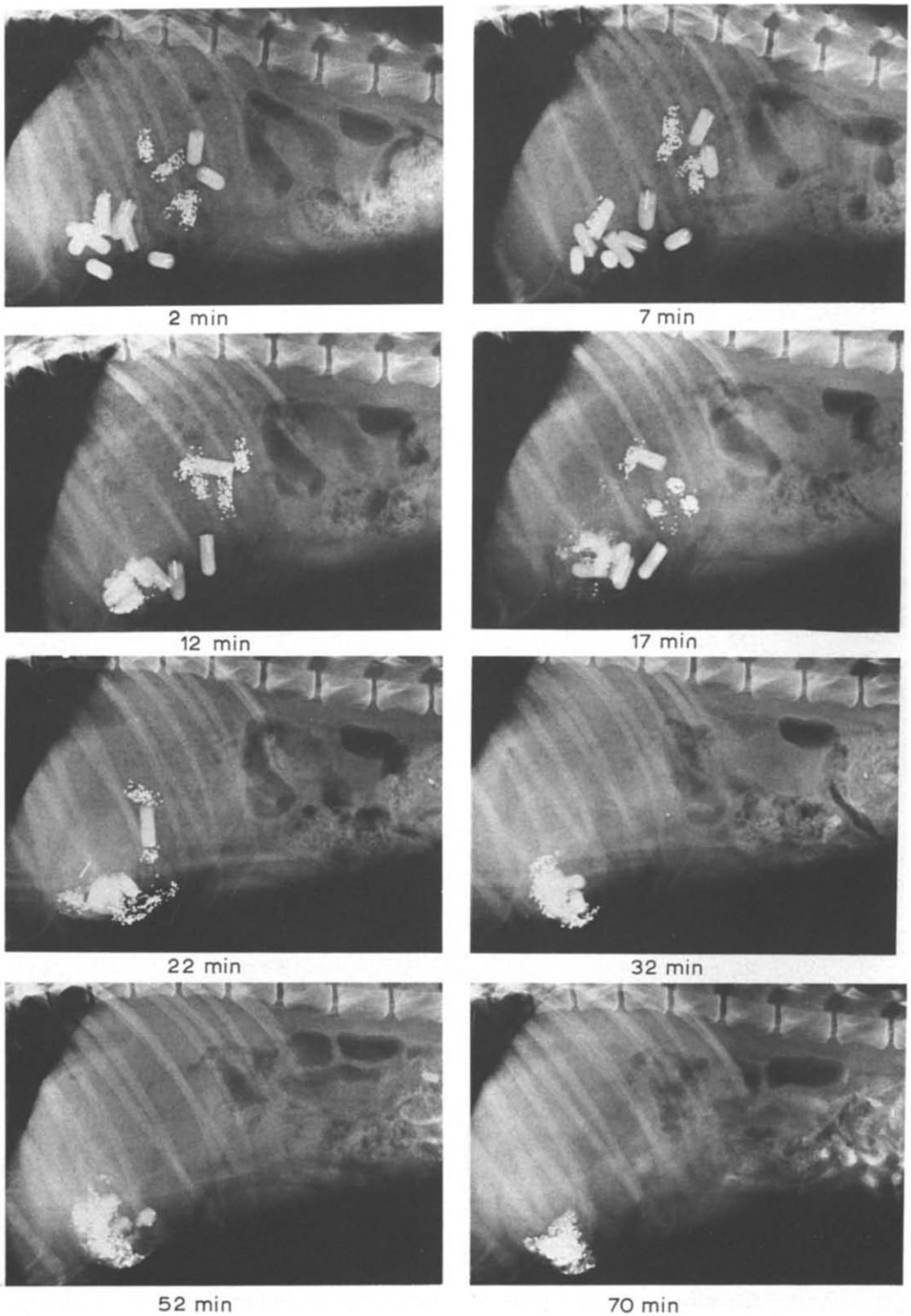

Fig. 1. The fate of 3 different capsule formulations in the stomach of a dog. Capsule contents: (1) ethylcellulose-coated pellets (capsules with pellets) (2) peanut oil + beeswax (capsules with rods), (3) polyethylene glycol 1500 (capsules without marker).

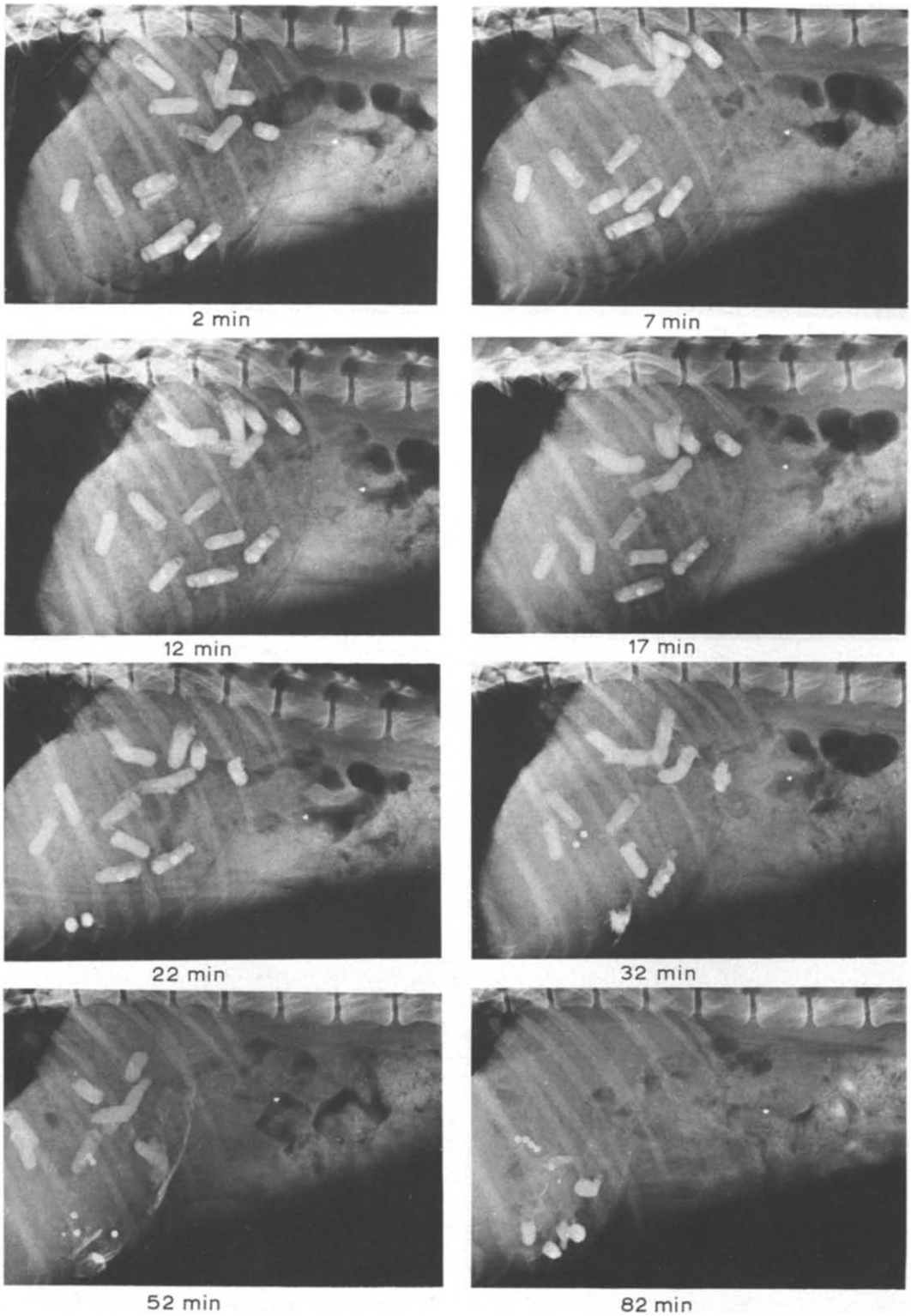

Fig. 2. The fate of 3 different capsule formulations in the stomach of a dog. Capsule contents: (1) lactose (capsules with balls), (2) corn starch (capsules with rods), (3) dicalcium phosphate (capsules without marker).

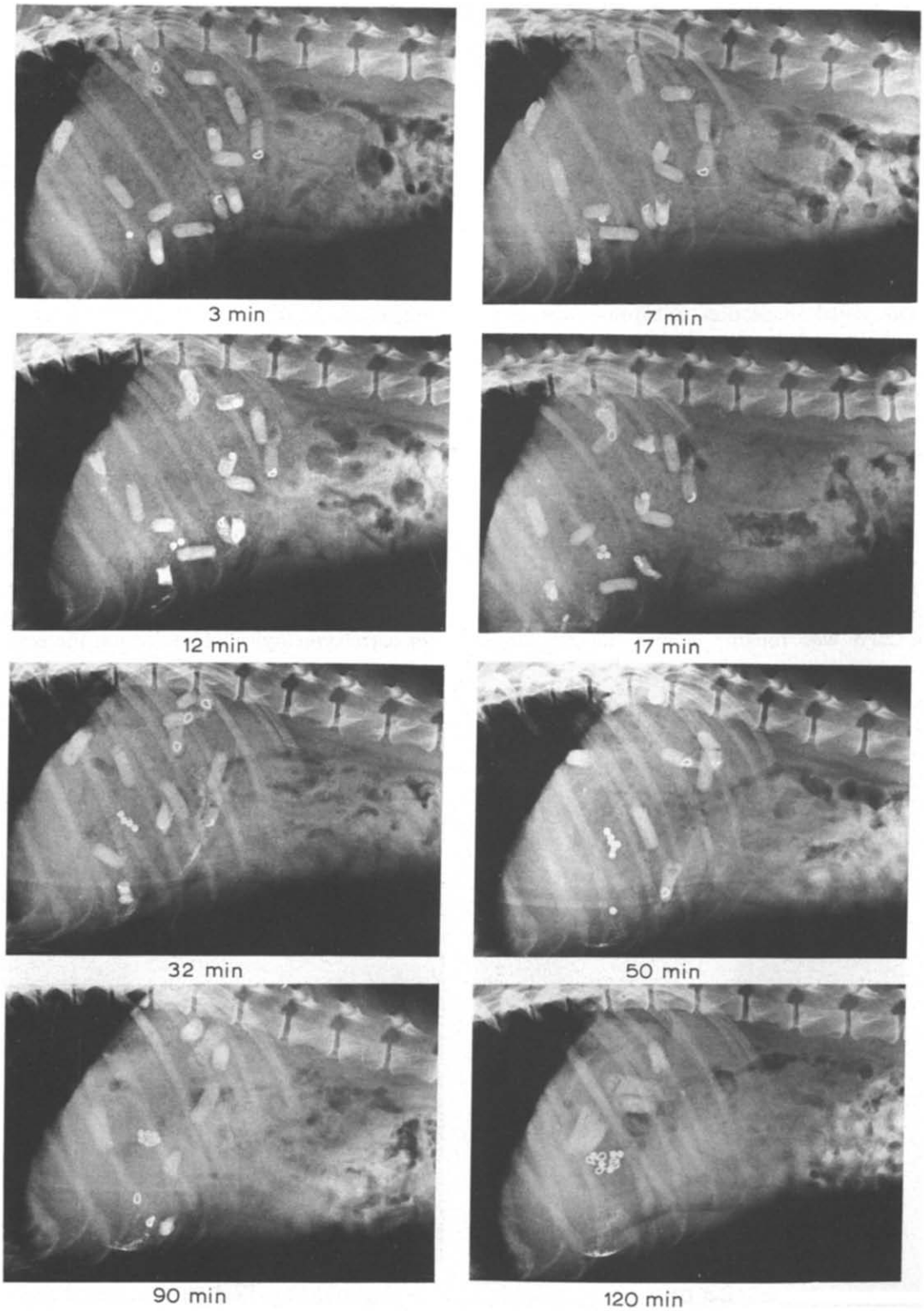

Fig. 3. The fate of 3 different capsule formulations in the stomach of a dog. Capsule contents: (1) sucrose (capsules with balls), (2) microcrystalline cellulose (capsules with rings), (3) carboxymethylcellulose sodium (capsules without marker).

In each experiment 5 capsules from each of 3 formulations were given to each dog, totalling 15 capsules. The tests were repeated at intervals of one week until all formulations had been tested in both dogs.

The commencement of feeding was taken as time 0. The first x-ray was taken immediately after feeding at 2–4 min. Thereafter x-rays were taken at 5, 10, 15, 20, 30 and 50 minutes. Where necessary further x-rays were taken at 20–30 min intervals. On visual inspection a capsule was considered to have disintegrated if the marker (ball, ring, rod or pellets) or barium sulphate content was seen outside the capsule. The time of disintegration was interpreted as having taken place at the midpoint between two consecutive x-rays.

Results

Regardless of capsule content, the mean disintegration time of the capsule shell in 0.1 M hydrochloric acid was roughly 1 min (largest range 40–75 s). The mean disintegration time in water varied from 1 to 2 min.

No marked difference in the in vitro disintegration time of the capsule shell was evident although widely different pharmaceutical additives were used. However, in capsules containing corn starch or carboxymethylcellulose sodium the contents of

TABLE 1

Effect of capsule content on the in vivo disintegration of hard gelatin capsules in the stomach of a dog; n = total number of capsules tested.

Content	Disintegration time, min		*n*
	Mean	Range	
Ethylcellulose-coated pellets	9	5–12	10
Sucrose	11	2–28	10
Lactose	14	7–25	10
Peanut oil + beeswax	21	15–42	8
Polyethylene glycol 1500	23	15–42	10
Microcrystalline cellulose	37	10–80	10
Dicalcium phosphate	44	22–67	10
Corn starch	> 90	44–	10
Carboxymethylcellulose	> 120		10

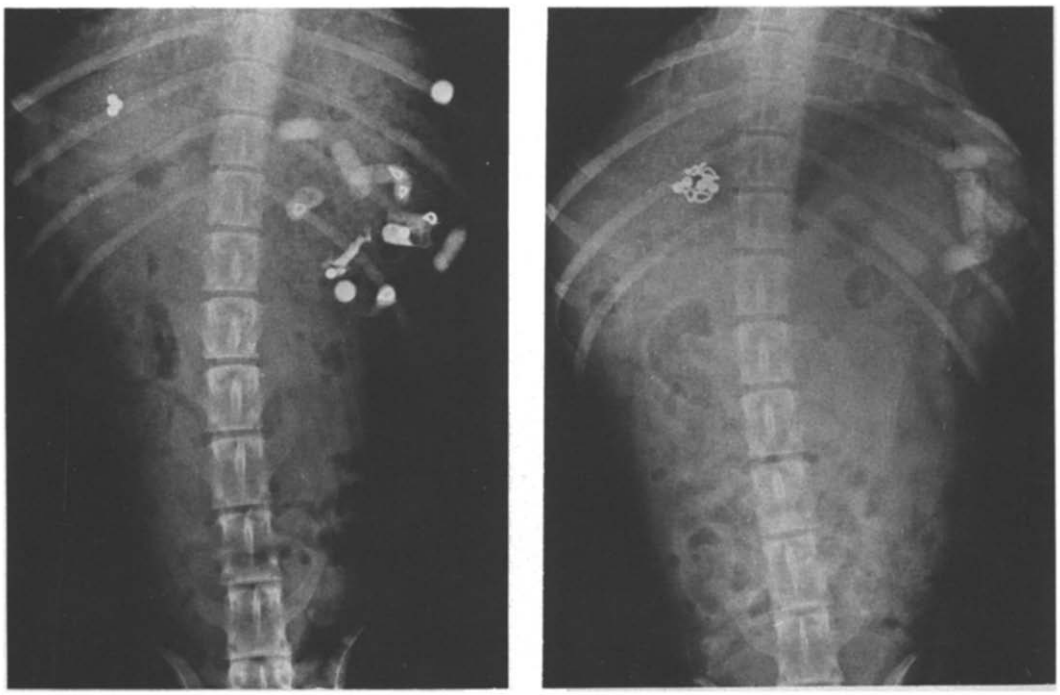

Fig. 4. Abdominal x-rays from the same dog as in Fig. 3.

the capsule formed a gelatinous matrix after disintegration of the shell. In the case of corn starch the matrix disintegrated in few minutes but it took longer than 30 min in the case of carboxymethylcellulose.

Figs. 1–4 show the fate of all formulations in the stomach of dog 1. Since both dogs showed similar disintegration times the results are combined in Table 1. Only eight peanut oil + beeswax capsules were observed since in one experiment dog 2 did not ingest all its food.

Discussion

The method described is useful for testing the in vivo disintegration of oral dosage forms in the dog, particularly where it is desired to test two or 3 different formulations simultaneously in the same animal. In our experience it is best to mark each different formulation with metal balls, rods or rings etc. in order to detect disintegration more easily. When a capsule contains coated barium sulphate pellets we recommend that the amount of radio-opaque pellets be no more than roughly 1/3 of the total content (Fig. 1).

The present method makes it possible to test 5–10 capsules simultaneously in the dog. Scintigraphic methods can study only a single tablet or capsule at a given time (Casey et al., 1976; Alpsten et al., 1979; Hunter et al., 1980). Parallel tests are important because the disintegration time of a capsule depends on its initial position in the stomach. The closer the capsule is to the antrum and pylorus the faster its disintegration (Figs. 1–3). This agrees with our previous results on the disintegration of enteric-coated products in the stomach of the dog (Marvola et al., 1986).

As seen in Table 1 there were marked differences in disintegration times in vivo, although in vitro the formulations behaved very similarly. With a highly water-soluble excipient such as sucrose or lactose, fairly rapid in vivo disintegration times (11–14 min) were obtained. This is in accordance with the results of Casey et al. (1976) who found that a capsule containing mainly lactose disintegrated in the empty stomach of a healthy volunteer at 6 min. With another formulation they found that in a full stomach much longer times were required. The present study was carried out under non-fasting conditions.

Sodium bicarbonate is also water-soluble, and capsules containing it have given in vivo disintegration times of 2.5 to 6 min (Eckert, 1967). An important factor which probably contributes to the rapid disintegration of sodium bicarbonate capsules is the formation of carbon dioxide. For the capsules containing sparingly water-soluble powder such as microcrystalline cellulose or dicalcium phosphate, the in vivo disintegration times were roughly 3 times as long as those obtained with sucrose or lactose. This agrees with the previous hypothesis that a water-insoluble content causes slower in vivo disintegration (Casey et al., 1976; Alpsten et al., 1979). The present results, however, indicate that water solubility is not the only important property in terms of disintegration. Although ethylcellulose-coated pellets are not water-soluble the capsules containing them disintegrated rapidly. This observation proves that a hard gelatin capsule constitutes the proper dosage form for controlled-release drug products consisting of numerous small subunits such as film-coated pellets. The subunits are released extremely rapidly from the capsule (Fig. 1).

Starches in general and corn starch in particular are often cited as being useful indifferent diluents in hard gelatin capsules with rapid drug release. In the present study, however, a very long disintegration time (exceeding 1.5 h) was obtained for capsules containing corn starch in non-fasted dogs (Table 1). Adherence of the capsules to the gastric mucosa was obvious since the capsules remained in the same position for a long period of time (Fig. 2). Observations that capsules may adhere to the gastric mucosa are in accordance with the findings of Hunter et al. (1980).

Even slower in vivo disintegration (Table 1) and more noticeable mucosal adherence (Fig. 3) were observed if the capsules contained carboxymethylcellulose. Such large amounts as those used here are, however, infrequent since carboxymethylcellulose is not a diluent but a binder of disintegrant. Typical concentrations range from 5 to 20%. However, the present results confirm that carboxymethylcellulose in hard gelatin

capsules is an effective combination for bioadhesive oral products.

According to the results, it is not the official pharmacopoeial disintegration test but rather a close observation of the behaviour of capsule contents following shell rupture that may provide valuable information concerning in vivo behaviour. In our prolonged disintegration test both corn starch and carboxymethylcellulose capsules formed a gelatinous matrix which did not disintegrate until long after rupture of the capsule shell. The same was observed in vivo, leading to a prolonged disintegration time and mucosal adherence.

It is possible that mucosal adherence is the result of two different mechanisms. Carboxymethylcellulose and starch are slightly water-soluble, swellable and gel-forming substances and can as such adhere to the mucosa. In addition, the interaction of additives with the gel-forming gelatin shell may increase the tendency of the formulation to stick to the gastric mucosa.

Adherence of a drug product to the gastric wall may be a harmful phenomenon if the drug substance has an irritating or ulcerative effect on the mucosa. Thus starches, carboxymethylcellulose and other gel-forming additives may be the wrong choice for conventional capsule formulations containing e.g. non-steroidal anti-inflammatory analgesics.

Capsules have also been reported to adhere to the oesophagus which, with certain drugs such as doxicycline, has led to oesophageal ulcerations or strictures (Bokey and Hugh, 1975; Crowson et al., 1976; Carlborg et al., 1978). Gelatin capsules and several gel-forming film-coating materials have also shown a clear tendency to stick to the oesophageal mucosa (Marvola et al., 1983; Kannikoski et al., 1984; Al-Dujaili et al., 1986). The present results, however, support the idea that the capsule shell is not the only important factor in adherence to the oesophagus. A gel-forming additive in the capsule may increase and a highly water-soluble ingredient decrease adherence. Thus for drug safety purposes it could be suggested that water-soluble additives be chosen for capsules containing drugs known to cause oesophageal injury.

Capsules with semisolid contents (polyethylene glycol 1500 or beeswax and peanut oil) disintegrated at roughly 20 min. There was no difference between the two formulations, although polyethylene glycol is water-soluble and beeswax and peanut oil are hydrophobic materials. Hunter et al. (1982) noted that capsules containing polyethylene glycol 1000 disintegrated in man in about 30 min.

All x-ray series show that the stomach of the dog was in the digestive mode during the experiment. None of the capsules or the markers released by them entered the intestine. This is clearly seen in Fig. 4, where the markers have accumulated in the vicinity of the pylorus, the capsules containing carboxymethylcellulose having adhered to the wall of the corpus. The markers were 3–4 mm in diameter and did not pass through the pylorus. This is in accordance with the findings that only particles smaller than 2 mm enter the duodenum of a dog during the digestive mode (Fara, 1985).

Conclusions

1. The present radiological method is useful for screening the in vivo disintegration of different oral formulations, particularly when two or 3 products are to be tested simultaneously.

2. The very similar disintegration of hard gelatin capsule shells in vitro does not form an accurate picture of the in vivo behaviour of the product. The behaviour of the capsule content once the shell has ruptured may, however, give some indication about in vivo disintegration.

3. If rapid drug release from hard gelatin capsules is desirable, highly water-soluble excipients are more favourable than water-insoluble ones.

4. Bioadhesive capsules can be made using swellable gelforming additives but in such cases the possible irritating effect of the drug should be taken into account.

5. A hard gelatin capsule constitutes a proper dosage form for controlled-release drug products consisting of numerous subunits.

6. The present results concern capsules filled manually. Where filling machines with plug formation are used the results may be different.

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