Pharmaceutical Research, Vol. 7, No. 11, 1990

Report

Gastrointestinal Transit of Nondisintegrating, Nonerodible Oral Dosage Forms in Pigs

Mohammad Hossain,[1] Wattanaporn Abramowitz,[1] Barbara J. Watrous,[2] Gregory J. Szpunar,[3] and James W. Ayres[1,4]

Received November 28, 1989; accepted May 11, 1990

Gastrointestinal (GI) transit data necessary as "baseline" or "control" information were collected using pigs as animal models preliminary to bioavailability studies of new sustained action formulations. Density and size effects of nondisintegrating dosage forms on GI transit were investigated. Initially, enteric-coated nondisintegrating magnesium hydroxide caplets (density, 1.5 g/ml; size, 19.6 × 9.5 mm; weight, 1.2 g) were utilized in seven pigs. Prolonged gastric residence (>5 days) occurred in every case for this dosage form. Therefore, nondisintegrating caplets of three densities (1.25, 1.45, and 2.3 g/ml) and three different sizes (large, 20 × 10 mm; medium, 10 × 10 mm; small, 5 × 10 mm) were studied in two more pigs. Roentgenography was used to visualize passage of caplets through the GI tract. Heidelberg pH capsules (size, 8 × 20 mm; density, 1.61 g/ml) were also used in this study. Total GI transit times range from 2 to 33 days for 22 administrations of these nondisintegrating dosage forms. Pigs are found to not be an appropriate model for evaluating bioavailability of nondisintegrating controlled-release dosage forms because total GI transit time (especially gastric transit) is much too long.

KEY WORDS: gastrointestinal transit; animal model; oral controlled release; nondisintegrating; plastic caplet; Heidelberg capsule.

INTRODUCTION

Gastrointestinal (GI) transit from mouth to colon has been estimated to be 8–10 hr, with transit being approximately 2–4 hr in the small intestine of man (1). Large tablets may empty rapidly (10–60 min) in undisintegrated form from a fasting stomach in people (2). Nondisintegrating devices designed to deliver drug over 24 hr may have emptied from the stomach, traversed the small intestine, and entered the colon in less than half that time (3). This could result in reduced systemic drug concentrations and a significant fraction of the dose being unabsorbed.

Hoelzel (1924), in his classic study of GI transit, showed that passage of substances through the digestive tract was proportional to their specific gravity (4). Bechgaard and Ladefoged suggested use of density to modify GI transit (5). However, Davis *et al.* concluded that gastric emptying of nondisintegrating single-unit oral dosage forms depends upon two major factors—the presence of food in the stomach and the size of the dosage form, not density (6). Gastric emptying of solutions and small pellets (<2 mm) occurs rapidly from fed stomach in humans, while larger single-unit systems are generally retained until the stomach is empty and then expelled during phase III contractions (7). Gastric emptying of particles smaller than 2 mm also occurs rapidly in fed dogs (8–11). It has been suggested that even smaller particles (<0.3 mm) would be required to be emptied from the stomach in the presence of food (12). Another report shows both size and shape influence movement of nondisintegrating dosage forms from stomach into intestine in dogs (13). However, some larger nondisintegrating tablets (3–7 mm) empty from the stomach of man during the digestive phase (14).

The interdigestive myoelectric complex (IMC), also known as the migrating myoelectric complex (MMC) (15–25), has been documented in dogs, pigs and humans. Gastric emptying of indigestible solids occurs in the fasting state in late phase II and early phase III MMC, with a periodicity of about 2 hr in humans and dogs (26–28). The MMC in pigs recur at intervals of 75–80 min (about 18/day) during fasting and with frequent but small meals (18). However, with one or two large meals per day, the postprandial contractile activity in pigs lasted 6 hr (13 MMC/day) or 3 hr (16 MMC/day), respectively. Propagation velocities of MMC in the proximal bowel of pigs, dogs, and humans have been reported to be 20.6 ± 2.4, 3.5–11.7, and 6.44 ± 0.74 cm/min, respectively (27,29,30).

Pigs have been widely used to study the rate of food passage through the alimentary tract (31–34). Each section of the GI tract of the pig is comparable anatomically to humans, and total-body weight ranges are similar (35). Man and swine

[1] College of Pharmacy, Oregon State University, Corvallis, Oregon 97331.
[2] College of Veterinary Medicine, Oregon State University, Corvallis, Oregon 97331.
[3] The Upjohn Company, Kalamazoo, Michigan 49001.
[4] To whom correspondence should be addressed.

0724-8741/90/1100-1163$06.00/0

have many biologic similarities, and therefore experimental data obtained with swine may be extrapolated to man (36). Food is normally emptied quickly from the stomach of pigs. About 30–40% of ingesta passes into the duodenum within 15 min in adult pigs (about 50–70 kg) (37) and passes through the stomach and small intestine much more rapidly than through the large intestine (38). Indigestible polyethylene tubing 2 mm in outside diameter and 2, 10, or 20 mm long resulted in the 20-mm units being retained significantly longer in the stomach (39,40).

If GI transit of nondisintegrating sustained-release products in pigs is similar to that in humans, then pigs would be a good model for bioavailability studies involving nondisintegrating controlled-release products. Specific objectives of this "baseline" study were

(1) to evaluate GI transit time of nondisintegrating prolonged-action dosage forms in pigs,
(2) to examine the effect of density and size of nondisintegrating dosage forms on GI transit in pigs, and
(3) to confirm adequacy of the model and determine whether it provides experimental results which can be extrapolated to humans.

EXPERIMENTAL

Subjects

Nine young adult female White Yorkshire pigs (6–8 months old) weighing approximately 45 kg were used. They were maintained on a commercially available Murphy Feed (Hog Ration 14) diet. The quantity fed was based on body weight (approx 6.5 g/kg/meal). The meal was fed twice a day, at 7:30–8:00 AM and 4:30–5:00 PM, moistened with water.

Housing

Pigs were housed and cared for by personnel at the Veterinary Teaching Hospital at the College of Veterinary Medicine. Animals were housed in small adjacent individual pens which have tubular metal divisions and rubberized wire mesh overlying concrete floors with a slope to facilitate regular washing and drainage of urine. The animal pens (2.32 m^2) allow reasonable space for free movement and normal activity of the pig to allow normal gastrointestinal motility. The housing area was kept lit during the daytime and dark at night.

Dosage Forms

Nondisintegrating magnesium hydroxide caplets (density, 1.5 g/ml; size, 19.6 × 9.5 mm; weight, 1.2 g) containing 15% bismuth as radiodense tracer (Table I) and enteric coated with hydroxypropylmethylcellulose phthalate were prepared. Heidelberg pH capsules (size, 8 × 20 mm; density, 1.61 g/ml) were also utilized.

Additional dosage forms consisted of caplet "blanks" of nonadhesive, nonwetting polymers, produced on a lathe from polymer block (Fig. 1). Plastic caplets were drilled and small stainless-steel rods inserted to help radiographic visualization and identification. Materials for caplet "blanks" were as follows: (i) low density, nylon (density, 1.25 g/ml); (ii) medium density, polyvinylchloride (density, 1.45 g/ml); and (iii) high density, Teflon (density, 2.30 g/ml). Nondisintegrating caplets of the above three densities were produced in caplet shape in the following three sizes: (i) large, 20 mm (long) × 10 mm (diameter); (ii) medium, 10 mm (long) × 10 mm (diameter); and (iii) small, 5 mm (long) × 10 mm (diameter).

Table I. Nondisintegrating Magnesium Hydroxide Caplet

Ingredients	Amount (mg)
Bismuth[a] granules	100.0
Carbopol 934[b]	44.0
Magnesium stearate[c]	16.5
Magnesium hydroxide[d]	1039.5

[a] Bismuth powder, 99.9999%, GOLD LABEL, Aldrich Chemical Co., Milwaukee, Wis.
[b] Carbopol 934, B. F. Goodrich Chemical Company, Division of the B. F. Goodrich Co., Cleveland, Ohio.
[c] Magnesium stearate (purified), Fischer Scientific Co.
[d] Magnesium hydroxide, Mallinckrodt, Inc., St. Louis, Mo. 63147.

Dosing

Each pig received all dosage forms by intubation on an empty stomach (after 12 hr of fasting) and were fasted 8 hr postdosing. All radiographs taken immediately prior to dosing showed the stomach to be empty.

After dosing, each pig was administered 15–20 ml water with an oral syringe. Otherwise, animals received their routine meals and free access to water. Food in the stomach was readily visible in radiographs taken following meals on subsequent days. Nondisintegrating magnesium hydroxide caplets were administered to each of seven pigs. In addition, the nine polymer caplets were each administered to two pigs for a total of 20 more administrations. Treatments with different size and density caplets were administered sequentially to each animal, each treatment (dosage form) given

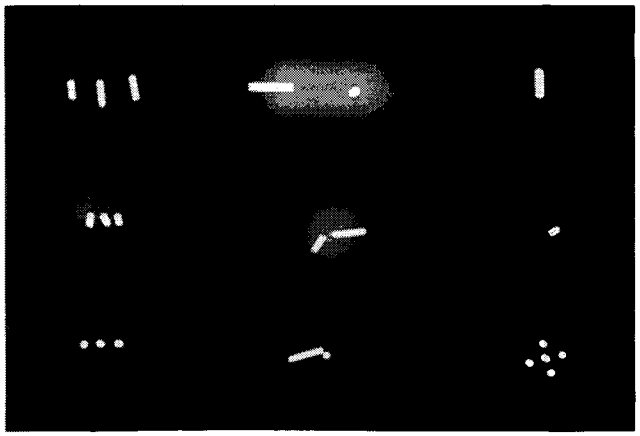

Fig. 1. X-ray photograph of dosage forms used in the study. Small stainless-steel rods inserted in dosage forms help radiographic visualization and identification. Left to right (density): Teflon, 2.30 g/ml; PVC, 1.45 g/ml; nylon, 1.25 g/ml. Top to bottom (size): large, 20 × 10 mm; medium, 10 × 10 mm; small, 5 × 10 mm.

after the previous dosage form had left the stomach and been in the small intestine for at least 24 hr.

Analytical Method

Roentgenography was used to follow passage of nondisintegrating caplets in the GI tract. Radiographs for pigs were exposed at 0 min (just before dosing to ensure an empty stomach), at 5 min (just after dosing to assure that the device was in the stomach), and then every 24 hr, since data from a pilot study revealed that gastric transit time required days.

For each animal, radiographic examinations were performed from two angles, a lateral view with a Fischer 41261G 300-mA mobile X-ray machine and a dorsoventral view with a GE DXR 1050 X-ray machine. Dupont Cronex 4 film with Dupont Quanta III screens were exposed at a distance of about 90 cm. Exposure settings were as follows: lateral view, 1/10 sec at 300 mA and 80 KVP; and dorsoventral view, 1/10 sec at 700 mA and 80 KVP. Standard animal posture and position were maintained during imaging using a minimum-stress Panepinto sling (Department of Physiology and Biophysics, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO 80523). Each pig was previously trained to stand quietly (supported by the sling) and to accept oral administration of water and was familiarized with the oral dosing gun. The minimum-stress experimental procedure serves to eliminate unnecessary discomfort to the animal and to normalize gastrointestinal activity.

RESULTS AND DISCUSSION

Orally administered nondisintegrating magnesium hydroxide caplets remained in the stomach for at least 5 days! This phenomenon was observed in 7 different pigs. After 5 days, the caplets started to dissolve in the gastric fluid even though they were enteric coated. Prolonged exposure to gastric acid and enzymes resulted in slow tablet disintegration and dissolution followed by passage into the intestinal tract. The surprising finding of prolonged gastric retention prompted study of GI transit using nondisintegrating, noneroding plastic caplets in two additional pigs.

There is a large amount of variability of GI transit with only two pigs (Table II), but prolonged retention in the stomach (days rather than hours) occurred consistently for 20 administrations of nondisintegrating plastic caplets just as it did for the enteric-coated magnesium hydroxide caplets in seven other pigs. Larger-size caplets had longer stomach emptying times and, therefore, longer total GI transit times. Gastric emptying time varied from 1 to 28 days and was often between 5 and 20 days for the plastic dosage forms in the two pigs.

Study with more animals would be necessary to determine if there is a consistent relationship between an increase in density and an increase in stomach emptying time for nondisintegrating caplets. Such experiments may be interesting but would not affect the obvious conclusion that gastric retention time in pigs is too long for pigs to be a good model for bioavailability studies involving nondisintegrating sustained-release dosage forms. Small intestine transit time was consistently less than 3 days and was less than 1 day for 50% of the doses (Table II).

Table II. Transit Time in Pigs for High-, Medium-, and Low-Density Nonerodible, Rigid Oral Dosage Forms Having Large, Medium, and Small Sizes

Subject	Density	Transit time (days)		
		Gastric	Small intestine	Large intestine
		Large caplet		
1	Low	1	<1	<1
2	"	5	<1	>2
1	Medium	10	2	19
2	"	5	1	1
	"	24[a]	<1	<1
1	High	13	2	4
2	"	5	2	3
	"	29[a]	<1	>3
		Medium caplet		
1	Low	4	<1	>1
2	"	4	<1	>1
1	Medium	2	1	3
2	"	1	<1	<1
1	High	7	<1	>3
2	"	5	2	1
		Small caplet		
1	Low	1	<1	>1
2	"	10	1	1
1	Medium	1	<1	<1
2	"	2	1	1
1	High	24	1	1
2	"	3	2	2

[a] Repeat experiment in same animal.

Nondisintegrating dosage forms were 100% retained in the stomach for 24 hr or longer in all nine pigs for all dosage forms studied. All caplets had a diameter of 5–10 mm and a density ranging from 1.25 to 2.30 g/ml. Cargill and coworkers recently found that nondisintegrating flexible Silastic disks having a very large diameter (25 mm) and a specific gravity of 1.13 were retained 47 to 67% in the stomach of beagle dogs for 24 hr (13). Smaller pellets were readily emptied from the stomach. Nondisintegrating tablets 3–7 mm in diameter and pellets 0.7–1.7 mm in diameter emptied from the stomach of people in 6 hr or less, depending on the size of the dosage form and whether the subject was fed or fasting (14,41–43). It has been suggested that gastric emptying time of nondisintegrating tablets (3–7 mm in diameter) in dogs or rabbits may be of little or no relevance to man (14). For the caplets studied herein, gastric emptying in pigs is even less relevant to man.

Heidelberg capsules were also administered to two pigs (after 12 hr of fasting) to measure GI transit and obtain *in vivo* GI pH values. Radiographs were used to locate the capsules. Heidelberg capsules had a gastric residence time in each of two pigs of >6 days (144 hr), a small intestinal transit time of >2 days, and a large intestinal transit time of >1 day. The gastric pH varied from 1.15 to 4.0. Two human volunteers also received Heidelberg capsules in this study after 12 hr of fasting. Gastric pH was 1.0–3.8 and gastric emptying time was 2.2–4.0 hr for these subjects. The range in gastric

pH (in both pigs and humans) may be attributed to the fact that sometimes the pH capsule works its way close to the pyloric sphincter, exposing its pH sensing membrane to duodenal juices. Then the capsule is retropulsed back into the stomach (18,44). However, the actual time of leaving the stomach is clearly indicated on the pH recording chart or radiograph.

Whereas stomach pH in pigs is similar to that in man (17,45), gastrointestinal transit time for nondisintegrating dosage forms is not. Gastric emptying of nonerodible caplets is found to be much slower in pigs (days) compared to humans (hours). Pigs have been reported (18) to possess a interdigestive, migrating myoelectric complex (MMC), which is known to play an important and dominant role in the gastric emptying of indigestible solids in man and dogs. The postprandial activity in pigs fed two meals per day lasts 2–3 hr and the average number of MMC was 16 to 18/day in fasting pigs (18). Even though it is possible that some of the pigs may have been dosed before arrival of the "housekeeper wave," the number of MMC during the 8 hr postdosing which occur when the stomach is empty should have been sufficient to empty the caplets from the stomach. However, from this GI transit study, it seems that such motor activity in pigs must be much less efficient in emptying large indigestible solids from the stomach in comparison to dogs or humans, or the mechanism in pigs may be entirely different. The capsule may have emptied with a phase III contraction, but certainly not the first antral phase III, or it may have emptied at a time other than phase III activity in the stomach. Ruckebusch and Bueno (1976) have shown that the postprandial pattern of electrical activity in pigs is characterized by almost continuous spiking activity in both the antrum and the small intestine, lasting 3–6 hr, depending on the volume and number of meals taken per day (18). Strong spike bursts are superimposed on each slow wave, some being propagated through the pylorus. The MMC is disrupted completely and occasional strong spike bursts, isolated or grouped, are propagated from the duodenal bulb at a high velocity and probably represent peristaltic activity of the stomach in the digestive mode. This may be responsible for causing a large object to be emptied randomly from the stomach. Thus, pigs are not an appropriate animal model for studying bioavailability or GI transit of nondisintegrating, nonerodible oral dosage forms.

ACKNOWLEDGMENT

The authors express sincere appreciation to Richard Kay for his excellent technical assistance for all radiographic work.

REFERENCES

1. H. S. Ch'ng, H. Park, P. Kelly, and J. R. Robinson. *J. Pharm. Sci.* 74:399–405 (1985).
2. A. F. Parr, R. M. Beihn, R. M. Franz, G. J. Szpunar, and M. Jay. *Pharm. Res.* 4:486–489 (1987).
3. R. Khosla and S. S. Davis. *J. Pharm. Pharmacol.* 39:47–49 (1986).
4. F. Hoelzel. *Am. J. Physiol.* 92:466–497 (1930).
5. H. Bechgaard and K. Ladefoged. *J. Pharm. Pharmacol.* 30:690–692 (1978).
6. S. S. Davis, A. F. Stockwell, M. J. Taylor, J. G. Hardy, D. R. Whalley, C. G. Wilson, H. Bechgaard, and F. N. Christensen. *Pharm. Res.* 3:208–213 (1986).
7. S. S. Davis, J. G. Hardy, and J. W. Fara. *Gut* 27:886–892 (1986).
8. J. H. Meyer, J. B. Thomson, M. B. Cohen, A. Shadchehr, and S. A. Mandiola. *Gastroenterology* 76:804–813 (1979).
9. J. H. Meyer, J. Dressman, A. Fink, and G. Amidon. *Gastroenterology* 89:805–813 (1985).
10. J. Russell and P. Bass. *Gastroenterology* 89:307–312 (1985).
11. T. Itoh, T. Higuchi, C. R. Gardner, and L. Caldwell. *J. Pharm. Pharmacol.* 38:801–806 (1986).
12. J. Heinamaki, M. Marvola, I. Happonen, and E. Westermarck. *Int. J. Pharm.* 42:105–115 (1988).
13. R. Cargill, L. J. Caldwell, K. Engle, J. A. Fix, P. A. Porter, and C. R. Gardner. *Pharm. Res.* 5:533–536 (1988).
14. R. Khosla, L. C. Feely, and S. S. Davis. *Int. J. Pharm.* 53:107–117 (1989).
15. H. Minami and W. McCallum. *Gastroenterology* 86:1592–1610 (1984).
16. R. A. Hinder and K. A. Kelly. *Am. J. Physiol.* 233:E355–E340 (1977).
17. C. Y. Lui, G. L. Amidon, R. R. Berardi, D. Fleisher, C. Youngberg, and J. B. Dressman. *J. Pharm. Sci.* 75:271–274 (1986).
18. Y. Ruckebusch and L. Bueno. *Br. J. Nutr.* 35:397–405 (1976).
19. I. De Wever, C. Eeckhout, G. Vantrappen, and J. Hellemans. *Am. J. Physiol.* 4:E661–E665 (1978).
20. I. R. Morris, P. H. Hammond, C. Darby, and I. Taylor. In M. Wienbeck (ed.), *Motility of the Digestive Tract,* Raven Press, New York, 1982, pp. 259–266.
21. G. L. Allen, E. W. Poole, and C. F. Code. *Am. J. Physiol.* 207:906–910 (1964).
22. G. Vantrappen. In M. Wienbeck (ed.), *Motility of the Digestive Tract,* Raven Press, New York, 1982, pp. 157–167.
23. P. Kerlin and S. Phillips. *Gastroenterology* 82:694–700 (1982).
24. P. Kerlin, A. Zinsmeister, and S. Phillips. *Gastroenterology* 82:701–706 (1982).
25. J. E. Kellow, T. J. Borody, S. F. Phillips, R. L. Tucker, and A. C. Haddad. *Gastroenterology* 91:386–395 (1986).
26. P. K. Gupta and J. R. Robinson. *Int. J. Pharm.* 43:45–52 (1988).
27. J. H. Szurszewski. *Am. J. Physiol.* 217:1757–1763 (1969).
28. M. Feldman, H. J. Smith, and T. R. Simon. *Gastroenterology* 87:895–902 (1984).
29. C. F. Code and J. A. Marlett. *J. Physiol.* 246:289–309 (1975).
30. D. Kumar, D. Wingate, and Y. Ruckebusch. *Gastroenterology* 91:926–930 (1986).
31. E. J. Castle and M. E. Castle. *J. Agr. Sci.* 47:196–203 (1956).
32. E. J. Castle and M. E. Castle. *J. Agr. Sci.* 49:106–112 (1957).
33. D. E. Kidder, M. J. Manners, and M. R. McCrea. *Res. Vet. Sci.* 2:227–231 (1961).
34. B. A. Ochia. *J. Physiol.* 233:467–480 (1973).
35. W. G. Pond and K. A. Houpt. *The Biology of the Pig,* Cornell University Press, Ithaca, N.Y., 1978.
36. R. O. McClellan. *Lab. Anim. Care* 18:120–125 (1968).
37. P. Auffrey and J. Martinent. *Ann. Biol. Anim. Biochem. Biophys.* 7:261 (1967).
38. J. E. Keys Jr. and J. V. DeBarthe. *J. Anim. Sci.* 39:57–62 (1974).
39. R. A. Argenzio and M. Southworth. *Am. J. Physiol.* 228:454–460 (1974).
40. E. T. Clemens, C. E. Stevens, and M. Southworth. *J. Nutr.* 105:759–768 (1975).
41. R. Khosla and S. S. Davis. *Int. J. Pharm.* 52:1–10 (1989).
42. M. Marvola, A. Kannikoski, H. Aito, and S. Nykanen. *Int. J. Pharm.* 53:145–155 (1989).
43. S. S. Davis, G. D. Parr, L. Feely, S. T. Leslie, S. Malkowska, and G. F. Lockwood. *Int. J. Pharm.* 49:183–188 (1989).
44. *Heidelberg pH Capsule System,* Training and Instructional Manual, 5th ed., May, 1985.
45. M. L. Kass, P. J. Van Soest, and W. G. Pond. *J. Anim. Sci.* 50:192–197 (1980).