J. Pharm. Pharmacol. 1986, 38: 801–806
Received March 10, 1986

Effect of particle size and food on gastric residence time of non-disintegrating solids in beagle dogs

TOMOH ITOH, TAKERU HIGUCHI, COLIN R. GARDNER*†, LARRY CALDWELL*

*Department of Pharmaceutical Chemistry, School of Pharmacy, University of Kansas, Lawrence, KS 66045, and *INTERx Research Corp. (Merck Sharp and Dohme Research Laboratories), 2201 West 21st Street, Lawrence, KS 66046, USA*

The gastric residence times of various sizes of radio-opaque particles and tablets were measured in beagle dogs by X-ray, both in the fasted state and after a single meal. During the course of the studies, changes in intragastric pH were also monitored with a radiotelemetric pH sensor, the Heidelberg capsule. The gastric residence time increased with increasing particle size and with particles ≥5 mm in diameter approached a plateau value both in the fasted state and after feeding. This value was about 7·5 h after feeding and about 1·5 h in the fasted state, and probably corresponded to the occurrence of the interdigestive migratory myoelectric complex (IMMC wave). The pH in the stomach was variable in the fasted state, but an abrupt pH increase (up to pH 6–7) was observed during the emptying of larger tablets. In some instances this high pH in the stomach was maintained until the next IMMC wave occurred. The gastric emptying of larger tablets administered with food was alo associated with an abrupt pH increase.

The effect of gastric emptying in the process of drug absorption has been pointed out for example by Levine (1970), Heading et al (1973) and Prescott (1974), and it is obviously a factor in the performance of enteric coated and sustained release dosage forms (Bogentoft et al 1978; Wilson et al 1984). With enteric coated products, gastric residence of the dosage form delays the onset of drug absorption. For sustained release dosage forms the transit time from mouth to caecum may limit the duration of drug absorption, since many drugs are more effectively absorbed in the small intestine than in the colon. Once the sustained release dosage form passes beyond the principal absorption site in the GI tract, any further drug released may not contribute to therapy. Thus, products which use either enteric or sustained release technologies may be only as predictable as the time of their emptying from the stomach.

Although there have been many studies on the gastric emptying of liquids, digestible solids and indigestible solids from physiological and nutritional standpoints, there has been limited interest in the gastric emptying of intact dosage forms (e.g. sustained release devices or enteric coated dosage forms). Mroz & Kelly (1977) reported that plastic spheres of 7 mm diameter emptied from the stomach as a bolus during the strong muscular contractions of the interdigestive migratory myoelectric complex (IMMC or 'housekeeper' wave). Hinder & Kelly (1977) and Meyer et al (1979) reported that digestible solids were broken down to particles of approximately 1 mm diameter before being emptied from the stomach, while larger non-digestible particles were retained. From these observations we might expect the gastric residence time of a given dosage form to depend on its size and its integrity. Non-invasive techniques such as external gamma-scintigraphy have been used to quantify differences in the behaviour of tablets and/or small pellets (Davis et al 1984; Kaus et al 1984), but in most such studies, simultaneous comparison of more than two different types of object has not been attempted.

In the present study we have examined the effect of particle size (1–10 mm) on the gastric residence time in dogs in fed and fasted states. We have also monitored the pH in the stomach during the course of the studies since this is a parameter which will influence the performance of pH-sensitive materials such as enteric coatings.

MATERIALS AND METHODS

Female beagle dogs were fasted for approximately 15 h. Dogs termed 'fasted' were not fed at any time during the experiments, while dogs termed 'fed' consumed 50 g of dog food at the beginning of each experimental period. Particles and tablets contained in size 000 gelatin capsules were orally administered to animals in the fasted state or 5 min after feeding. Radio-opaque particles (1–3 mm in diameter) were obtained by mixing powdered low-density polyethylene (Aldrich Chemical Co., Inc.) with barium sulphate ($BaSO_4$) 30% w/w and extruding at 200 °C. Rods of radio-opaque material which were of 1, 2 or

† Correspondence to MSD Research Laboratories, West Point, PA 19486, USA.

3 mm diameter, were cut into 1, 2 and 3 mm lengths, respectively, to obtain small cylinders of the appropriate dimensions. Ten of each size were administered at one time. Radio-opaque tablets (4·7–10 mm in diameter) were obtained by tableting $BaSO_4$ powder with microcrystalline cellulose powder (Avicel pH 101) and corn starch using a wet granulation technique, then coating these tablets with either hydroxypropylmethylcellulose-phthalate (HPMCP), (Shin-etsu Chemical, Type HP-50) or cellulose acetate (CA; Eastman, Type CA-398-10). Five of each size were administered at one time. The amount of $BaSO_4$ was 30–40% of the total weight of the tablets.

The pH in the stomach was measured with a radiotelemetric pH sensor, the Heidelberg capsule (Telfunken, West Germany). A surgical suture was tied to each Heidelberg capsule before oral administration, allowing the sensor to be tethered and ensuring that the sensor would not be expelled from the stomach into the small intestine during the course of the experiment. Thus, the pH in the stomach could be monitored continuously during the emptying process of particles and tablets.

The Heidelberg capsules were allowed to soak in water for 30–45 min before initial calibration. In many of the experiments the capsule was withdrawn from the stomach at the end of the study and re-checked for validity of the measurements. In no case did the post-study value differ by more than 1 pH unit from the initial calibration (i.e. within the manufacturer's specifications). On a few occasions the Heidelberg capsule was cut free at the end of the experiment and later recovered from the faeces. Even in these instances the calibration was still reasonable 25–30 h after administration.

Following administration of the particles, the dogs were X-rayed every 2–3 min for the first 15 min then at 15 min intervals to determine the location of the particles. The outline of the stomach showed up sufficiently clearly on the film to permit definitive gastric location of the particles. The individual particles and tablets were identified and their position recorded for later analysis. Each of three dogs were studied on a number of occasions using either 5 or 10 particles of each size as described above.

RESULTS AND DISCUSSION

Fasting state

Fig. 1 shows a typical pH profile in the fasting stomach. There were generally periodic fluctuations in the pH readings, some of which may have been artifactual due to movement of the capsule in the stomach. However, there were also periodic, abrupt and sustained pH elevations (up to pH 6–7) during which a strong pulling force (>10 g) was noted at the suture tied to the Heidelberg capsule. During the course of the experiment, X-radiographs demonstrated the capsule was free to move within the stomach and, that following the strong contractions, it was still to be seen in the gastric pouch. In no case was a tethered capsule observed to have passed the pylorus into the duodenum. In some instances a capsule with a suture attached was permitted to pass into the duodenum. Pulling forces were not encountered under these conditions, suggesting that the duodenal contractions were weaker than those of the stomach. Larger tablets (5–10 mm diam.) were emptied from the stomach during the abrupt pH increase, indicative of the IMMC activity, but smaller particles (1–3 mm diam.) were emptied in a more random fashion, sometime before this abrupt pH increase

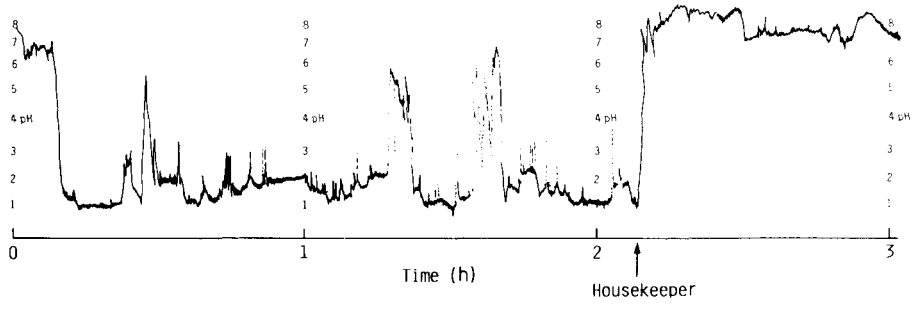

FIG. 1. Typical intragastric pH-time profile in the fasted beagle dog as measured by the Heidelberg capsule. At the time indicated by the arrow large particles were observed by X-ray to exit the stomach 'en masse' indicating the occurrence of an IMMC wave. In the case shown here the elevated pH associated with the IMMC was maintained for more than 1 h.

occurred. After this abrupt pH increase, in some instances the pH in the stomach gradually diminished to a value of pH 1–2, while in other instances the high gastric pH was maintained for long periods (1–2 h).

In order to verify the reliability of the pH measurements recorded by the Heidelberg capsule, gastric juice samples were aspirated via a tube inserted into the stomach through the mouth, and the pH of the sampled gastric juice was measured with a conventional pH meter. A piece of copper foil was attached to the end of the intragastric tube to check with X-ray the position of the sampling port relative to the Heidelberg capsule. Gastric juice samples were aspirated separately during low pH readings and during the high pH readings. The results are summarized in Table 1. Considering the manufacturer's specifications of the Heidelberg capsule, there is good agreement between the two sets of values.

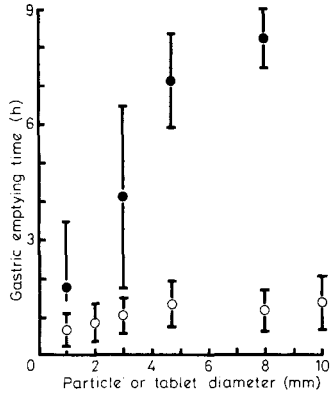

FIG. 2. Mean emptying times of radio-opaque particles and tablets as a function of particle size in the beagle dog. (●) after feeding and (○) fasting. Error bars are standard deviations. n, the number of particles. After feeding: 1 mm, n = 99; 3 mm, n = 110; 4·7 mm, n = 110; 8 mm, n = 30. Fasting: 1 mm, n = 120; 2 mm, n = 60; 3 mm, n = 60; 4·7 mm, n = 236; 8 mm, n = 60; 10 mm, n = 45.

Fig. 2 shows the gastric emptying time of various sized particles and tablets as a function of size and state of feedings. In the fasted state, the mean gastric emptying time increased with an increase in size, approaching a plateau at about 1·4 h for tablets with a diameter of 5 mm or greater. Since the positions of the particles were monitored intermittently, it was not possible to determine the exact time of emptying and correlate it with the pH at the instant of emptying. However, the emptying time obtained with the larger particles corresponded to the time at which the abrupt increase in pH was observed. The emptying profiles for all the particles are shown in Fig. 3. When the particles were observed to have passed the pylorus, the pH at which this occurred was taken as the average of the value at that time point and the pH value at the previous X-ray time point. Thus, since the pH usually increased at emptying, the pH values used in Fig. 3 are probably underestimates of the pH at the time of emptying, particularly for the larger tablets. The results in Fig. 3 show a tendency for the smaller particles to empty from the stomach at low pH (i.e. in the absence of housekeepers) while the larger tablets emptied predominantly at the higher pH values which were associated with the occurrence of IMMCs.

Table 1. pH of aspirated gastric juice samples.

	pH in the stomach (Heidelberg capsule)	pH of an aspirated gastric juice sample measured with a pH meter
Dog 1	1·0	1·37
	5·5–6·0	6·68
Dog 2	1·0	1·25
	1·0–1·5	1·63
	5·5–6·5	7·48
Dog 3	1·0	1·62
	6·0	6·66
	5·5–6·0	7·00

Our results confirm the observation of Mroz & Kelly (1977), that larger tablets empty from the stomach only with the IMMC wave, and in the dog, the housekeeper seems to be associated with an abrupt pH increase in the stomach. Smaller particles, however, emptied with weaker contractions of the stomach at relatively low pH values in a manner similar to small particles of food during normal digestive activity (Hinder & Kelly 1977).

The abrupt pH increase may be due to either reflux from the duodenum or some other means of local neutralization of stomach acid. The fact that in some cases, the high pH (5–7) was maintained until the next IMMC effect occurred implies that, at least in those cases, there was minimal acid secretion in the stomach after the IMMC activity. This would be consistent with the fact that the dog is known to have a low basal rate of gastric acid secretion (Konturek et al 1977).

Fed state

Fig. 4 shows the typical pH profile in the stomach after feeding. There was a mildly acid pH region

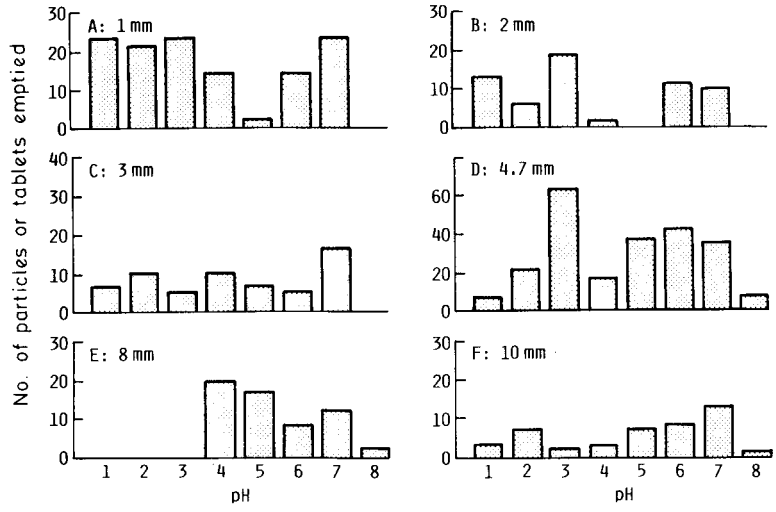

FIG. 3. Frequency of particle emptying in the fasting beagle dog as a function of the intragastric pH at the time of emptying. Different particle sizes are represented: (a) 1, (b) 2, (c) 3, (d) 4·7, (e) 8, (f) 10 mm.

observed after feeding which may reflect the buffering capacity of the food, followed by a steady state low pH for some hours. Eventually there was an abrupt pH increase which corresponded to the occurrence of the IMMC. We again observed the gastric emptying of smaller tablets before the abrupt pH increase and that of the larger tablets during the abrupt pH increase. The most significant difference between the fed and the fasting state, was that feeding even a small meal postponed the IMMC effect for many hours. Fig. 2 shows the gastric emptying time of various sizes of particles and tablets as a function of size after feeding. The gastric emptying time again increased with an increase in

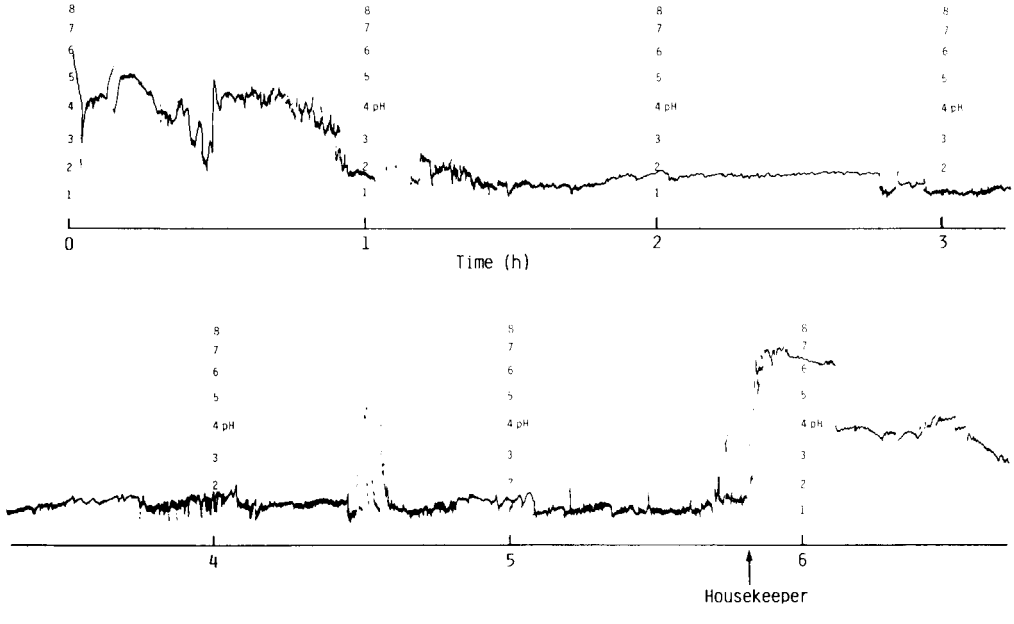

FIG. 4. Typical intragastric pH-time profile in the beagle dog after a single meal (50 g standard dog chow), as measured by the Heidelberg capsule. As in Fig. 1, the arrow indicates the occurrence of a 'housekeeper' identified by gastric expulsion of large particles. The elevated pH observed at this time slowly declined over the course of the next hour.

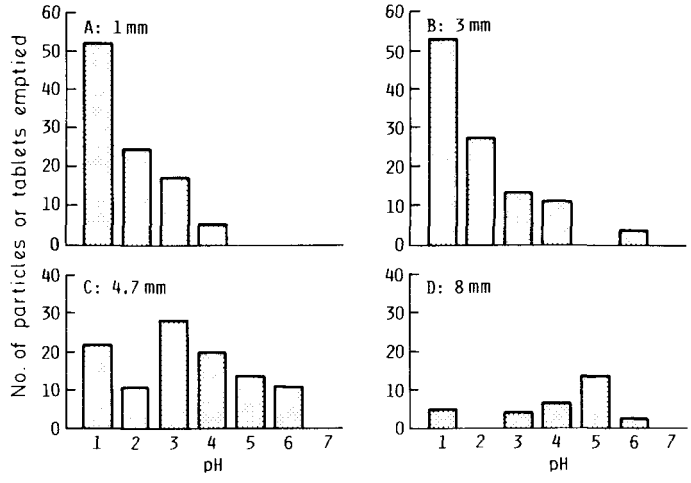

FIG. 5. Frequency of particle empyting as a function of intragastric pH in the beagle dog after a single meal (50 g wet weight). Different particle sizes are represented: (a) 1, (b) 3, (c) 4·7, (d) 8 mm.

particle size and approached a plateau for particles 5 mm or greater. This value occurred at approximately the same time as the abrupt pH increase. The gastric emptying time of all the particles and tablets after feeding was significantly greater than in the fasting state, except with the 1 mm particles.

Fig. 5 shows the pH at which the particles or the tablets emptied from the stomach after a single meal. Again, the pH values shown are the averages of the minimum and maximum pH during the gastric emptying process. The tendency for smaller particles to empty at lower pH and larger tablets to empty at higher pH was more marked after feeding than in the fasting state. These results again strongly suggest that the large tablets (5–10 mm diam.) emptied from the stomach only during the strong contractions from the IMMC, but that the small (1–3 mm diam.) behaved more like digestible food and emptied from the stomach with weaker contractions before the IMMC wave occurred.

According to our results with Beagle dogs, the pH in the stomach varied between 1 and 7 in the fasting state and sometimes the higher pH was maintained for prolonged periods. Since enteric coated dosage forms are designed to dissolve rapidly at neutral pH, these coating materials might dissolve in the stomach during periods of high pH, with a hypothetical acid-labile drug being subject to decomposition during the ensuing acidic pH period. If similar pH fluctuations should exist in the human stomach, this may be one factor contributing to the large bio-variability sometimes seen with enteric dosage forms.

In the fed condition, smaller dosage forms (1–3 mm diam.) emptied from the stomach well before the period of pH fluctuation began, while larger dosage forms (5–10 mm diam.) emptied during or after the onset of a pH rise. These observations suggest that smaller enteric coated particles should be more dependable in their gastric emptying profile compared with larger monolithic forms, and thereby reduce variations in bioavailability of acid-labile drugs.

Since even large dosage forms emptied from the stomach within 1·5 h in the fasting state, the administration of a sustained release dosage form in the fasting state could result in less than optimum bioavailability if the dose form is designed to deliver drug for an extended period. Because drug absorption is often limited to the small intestine, drug molecules which are released in the stomach or within the small gut may be efficiently absorbed while drug molecules which are released after the dosage form passes into the large bowel may not contribute to therapy. After a single small meal a large dosage form (more than 5 mm diam.) was retained in the dog stomach for 7·5 h. Larger sustained release devices may therefore offer continuous drug absorption for as much as 10 h after eating, assuming 3–4 h for small intestinal transit time. In man, the retention time of a larger dosage form in the stomach has been demonstrated to be

dependent on the calorific content of meals and frequency of eating (Mojaverian et al 1985). Data from a human study addressing some of the issues raised by the present dog study would be of value in designing more effective dosage forms.

REFERENCES

Bogentoft, C., Carlsson, J., Ekenved, G., Magnusson, A. (1978) Eur. J. Clin. Pharmacol. 14: 351–355

Davis, S. S., Hardy, J. G., Taylor, M. J., Whalley, D. R., Wilson, C. G. (1984) Int. J. Pharmaceutics 21: 167–177

Heading, R. C., Nimmo, J., Prescott, L. F., Tothill, P. (1973) Br. J. Pharmacol. 47: 415–421

Hinder, R. A., Kelly, K. A. (1977) Am. J. Physiol. 233: E335–E340

Kaus, L. C., Fell, J. T., Sharma, H., Taylor, D. C. (1984) Int. J. Pharmaceutics 20:315–323

Konturek, S., Rayford, P., Thompson, J. (1977) Am. J. Physiol. 233: E537–E543

Levine, R. R. (1970) Am. J. Dig. Dis. 15: 171–188

Meyer, J. H., Thomson, J. B., Cohen, M. B., Shadchehr, A., Mandiola, S. A. (1979) Gastroenterology 76: 804–813

Mojaverian, P., Ferguson, R. K., Vlasses, P. H., Rocci, M. L., Oren, A., Fix, J. A., Caldwell, L. J., Gardner, C. R. (1985) Ibid. 89: 392–397

Mroz, C. T., Kelly, K. A. (1977) Surgery 145: 369–377

Prescott, L. F. (1974) Br. J. Clin. Pharmacol. 1: 189–190

Wilson, C. G., Parr, G. D., Kennerley, J. W., Taylor, M. J., Davis, S. S., Hardy, J. G., Rees, J. A. (1984) Int. J. Pharmaceutics 18: 1–8