International Journal of Pharmaceutics, 43 (1988) 45–52
Elsevier

IJP 01443

Gastric emptying of liquids in the fasted dog

Pardeep K. Gupta and Joseph R. Robinson
School of Pharmacy, University of Wisconsin, Madison, WI 53706 (U.S.A.)

(Received 18 June 1987)
(Modified version received 18 September 1987)
(Accepted 12 October 1987)

Key words: Stomach; Discharge; Motility; Fasted state; Water; pH

Summary

Gastric emptying of different volumes of water was studied in the fasted dog. Volumes of water ranging from 25 ml to 500 ml at 20 °C were administered during phase I of the fasted state by natural swallowing. Effluent was collected from a permanent Thomas cannula located in the duodenum about 15 cm from the gastroduodenal junction. The presence of phase I was ascertained by observing the discharge from the cannula prior to administration of water. Mucus and bile discharge was taken as phase II activity, and 20 min after cessation of any discharge motility was assumed to be phase I. Distinctly different patterns of fluid discharge were observed for volumes smaller than and larger than 100 ml. For small volumes a lag phase was observed before the discharge of stomach contents, with most of the discharge occurring at the onset of and during phase II. Large volume discharge on the other hand followed characteristic first-order kinetics, a finding consistent with many studies already reported in the literature. The results indicate that the stomach emptying pattern of water depends on the administered volume. While small volumes follow the existing motility pattern in the stomach, large volumes convert the stomach activity to a continuous 'fed like' state and result in a continuous discharge of liquid until most of the liquid is discharged and the fasted state is subsequently restored. The change of time required for discharge of half of the administered volume from 40 min to 10 min for small to large volumes suggests that this transition in the discharge patterns occurs between 100 and 150 ml for water in the fasted dog. Additional findings of this study are the pH changes associated with the different volumes of water. The pH of duodenal discharge was between 7 and 8 for small volumes and decreased progressively as the volumes were increased, being as low as 1.5 when 500 ml water was administered, indicating that large volumes apparently induce acid secretion in the stomach.

Introduction

Since the success of an oral dosage form depends in part on its processing within the environment of the gastrointestinal tract, characterization of the biological variables in this organ is of importance to the design and evaluation of oral drug delivery systems. The importance of the transit patterns of solids and liquids for oral controlled drug delivery systems is evidenced by the volume of literature on this subject. Considering that there are two distinct modes of gastrointestinal motility patterns, fasted and fed, in humans and animals that consume food on a discrete basis (Jacoby et al., 1963; Weisbrodt, 1981) transit pattern of dosage forms and liquids and hence the bioavailability of orally administered drugs may be different depending on whether the medications are given in the presence or absence of food.

The fasted gastrointestinal motility pattern is characterized by a cyclic pattern in both dog and

Correspondence: J.R. Robinson, School of Pharmacy, University of Wisconsin, 425 North Charter Street, Madison, WI 53706, U.S.A.

TABLE 1

Interdigestive migratory motor complex in dog and man

	Duration (min)		Fluid discharge in both species	Reference
	Dog	Man		
Phase I	40– 65	50– 60	none	(Miolan and Roman, 1978)
Phase II	15– 20	20– 40	bile and mucus	(Gill et al., 1985)
Phase III	10– 15	15– 20	bile and mucus	(Gill et al., 1985)
Phase IV	6– 16	–	mucus	(Miolan and Roman, 1978)
One cycle	90–120	90–120		(Miolan and Roman, 1978; Gill et al., 1985)

man (Szurszewski, 1969; Vantrappen et al., 1977), each cycle lasting about 90–120 min in both species (Kerlin, 1982). This cyclic interdigestive pattern which originates in the foregut and propagates to the terminal ileum can be divided into 4 distinct phases: phase I, representing a quiescent period with no spike activity and no contractions; phase II, the period of random spike activity or intermittent contractions; phase III, the period of regular spike bursts or regular contractions, at a maximal frequency that migrate distally; and phase IV, the transition period between phases III and I (Code and Marlett, 1975). Upon feeding, this interdigestive migratory motor complex (IMMC) is interrupted and is replaced by continuous contractions of medium intensity. Table 1 describes the relative lengths of various components of the fasted phase activity.

Another major cyclic event associated with the fasted activity is the secretory component. In dog, the increased gastric motility is accompanied by a periodic increase in mucus, biliary and pancreatic secretion in the absence of any other secretory stimulation (Vantrappen et al., 1979). There are little or no secretions during phase I. Bile enters the duodenum during phase II (Traynor et al., 1984) while mucus discharge occurs from the stomach during the latter part of phase II and all of phase III (Reinke et al., 1967). Thus appearance of bile and mucus can serve as an indirect indicator of the existing phasic motor activity during the fasted state.

Most bioavailability studies are performed after an overnight fast and a specified volume of water is typically coadministered with the dosage form. However, no studies are available regarding the fate of small volumes of liquids given with the dosage form. Fluid dynamics and mixing characteristics in the GI tract can have a profound influence on the transit pattern and distribution of a dosage form. The extent of gastrointestinal secretions can present dissolution and stability problems for the drug, as well as influence its dissolution and hence its absorption characteristics. A number of studies have reported different plasma drug profiles for a variety of drugs including theophylline when given with small or large volumes of water (Welling, 1980; Nimmo, 1980).

Gastric emptying of liquids has been studied and reported extensively during the last 35 years. Hunt and MacDonald (Hunt and MacDonald, 1954; Hunt, 1959) have reported that gastric emptying of liquids follows first order kinetics, the slope of the curve depending on the nature of the liquid. When coadministered with solids, liquids empty faster (Thomas, 1957; Rees et al., 1979) and maintain their first-order kinetic discharge. None of the studies reported a relationship between antral motility and liquid discharge, presumably because the volumes given were large enough to change the motility pattern to a consistent continuous motility (Camillarim et al., 1985). However, the proximal stomach has been reported to regulate the stomach emptying of liquids (Kelly, 1980). Among the factors which influence stomach emptying of liquids are viscosity (Russell, 1985), meal temperature (Bateman, 1982), disease state (Jian et al., 1984) and age (Kupfer et al., 1985). However, all of the available studies have a physiological perspective and primarily involve large volumes of test meals. There is no study available to date on the fate of small volumes of liquids administered in the fasted state.

Previous studies from this laboratory have indicated that small volumes of normal saline (50 ml) follow the existing motility pattern (Gruber et al., 1987). The present study was aimed at studying the stomach handling of different volumes of water ranging from 25 ml to 500 ml. Test meals were administered during phase I to observe the influence of the phasic activity on small volumes of water and to determine the volume at which the transition of the discharge pattern occurs from small to large volumes. Also the change in the secretory activity of the stomach, particularly acid, was explored as a function of the administered volume. The dog was chosen as an animal model because of the similarity of its GI motility to humans (Dressman, 1986), is extensive use in pharmacokinetic studies and convenience of handling.

Materials and Methods

Three adult, female dogs of mixed breed, weighing 15-20 kg., were used in the study. Each dog was prepared with a permanent duodenal cannula.

Dog preparation

As reported in the previous studies from this laboratory (Gruber et al., 1987) the surgical procedure of Reinke et al. (1967) was followed to implant the cannula into the duodenum. After being anesthetized with 30 mg/kg of sodium pentobarbital (Nembutal sodium solution, 50 mg/ml; Abbott Laboratories, North Chicago, IL), the dogs underwent laparotomy under asceptic conditions. A modified Thomas cannula made of Derlin (o.d. 17 mm, i.d. 16 mm; The University of Wisconsin Physical Plant Machine Shop, Madison, WI) was implanted in the duodenum through a longitudinal cut about 15 cm from the gastroduodenal junction on the side free of mesenteric blood supply. The cannula was exteriorized through an opening in the abdomen and fixed to the abdominal wall at a site about 4 cm below the last rib and 2.0 cm from the midline cut. A recovery period of two weeks was allowed before the animals were used for studies. The dogs were trained to stand quietly, supported by slings (Alice King Chathman Medical Arts, Los Angeles, CA) and to accept oral administration of liquids by natural swallowing.

Administration of water

Prior to each experiment, the dogs were fasted for 16–18 h with free supply of water. In order to use the bile and mucus discharge to ascertain phasic activity, the cannula was opened and duodenal discharge allowed to drain. If bile and mucus discharge was observed on opening the cannula, then the arrival of the next phasic activity was awaited to time the first arrival of bile. After one complete phasic activity cycle was over, an additional 20-min period of no discharge was allowed in order to make sure that the GI motility of the dog was in phase I. At this time, which was arbitrarily taken as time zero, the required volume of tap water at 20 °C was instilled into the back of the dog's mouth by a flexible tube (5 mm i.d.) attached to a 200-ml syringe. The dog's mouth was held up and water instilled at a rate of about 250 ml/min which was swallowed comfortably.

Duodenal effluent collection

Following administration of water, all duodenal effluent was collected from the cannula at 2-min intervals until 10 min and then at 5-min intervals. This included the volume discharged from the stomach as well as the secretions of the first 15 cm of duodenum. The effluent was collected until the end of the next phasic activity (about 120 min) and its volume and pH (Digital pH/mV meter, model 701A, Orion Research, Cambridge, MA) determined. Three repetitions at each volume were carried out on each dog, and the data from three dogs was pooled to calculate the mean and standard error of the mean. Total effluent from one complete phasic activity prior to which no volume was administered was also collected on many occasions to compared the volume and pH with the effluent after administration of water.

Results and Discussion

Liquid discharge

Onset of discharge from the cannula was observed after a lag of 1–3 min following adminis-

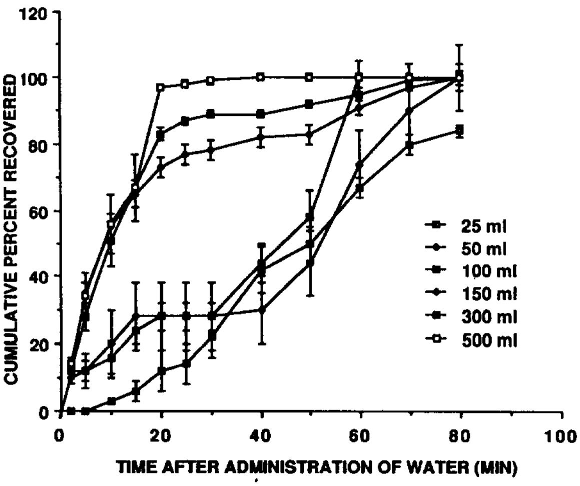

Fig. 1. Gastric emptying of different volumes of water (25–500 ml) given 15–20 min after cessation of high antral activity in fasted dogs. Error bars are S.E.M. of 9 trials.

tration of 150 ml, 300 ml, and 500 ml water. As is evident from Fig. 1, the cumulative percent volume discharge shows an exponential type curve which becomes more obvious when plotted as cummulative total volume recovered (Figure 2). Most of the administered volume is discharged during 20 min after administration, with roughly half being discharged in about 10 min. This discharge is then followed by a period during which there is little or no effluent from the cannula, indicating that phase I activity has returned. 40-60 min after administration bile discharge starts at the onset of the next phase II activity followed by mucus and the fasting cycle is subsequently restored. The onset and pattern of discharge of all 3 volumes were very consistent within an animal and varied slightly among 3 dogs. In no case was the lag time larger than 3 min and the total discharge time less than 30 min.

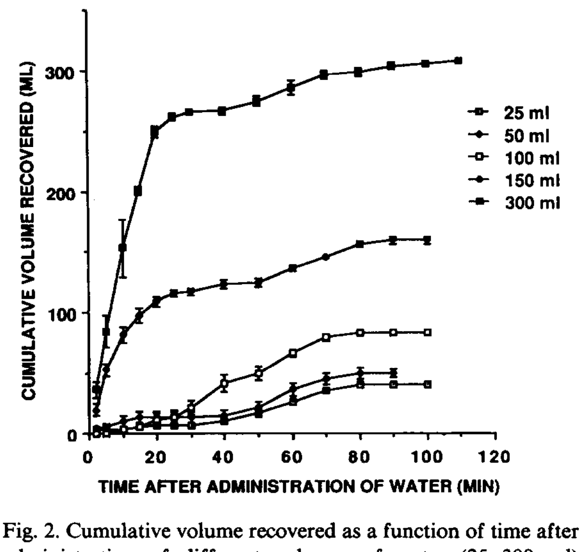

Fig. 2. Cumulative volume recovered as a function of time after administration of different volumes of water (25–300 ml) 15–20 min after cessation of high antral activity in fasted dogs. Curve for 500 ml water has been left out for the sake of clarity. Note the change in the discharge pattern between 100 and 150 ml.

Discharge of smaller volumes on the other hand followed a completely different pattern. Following administration of 25, 50, and 100 ml of water, there was little or no discharge during the next 20–30 min. This was followed by a continuous effluent flow from the cannula around the time the next phase II activity was due. Thus most of the 100 ml or less water administered was discharged at the onset of phase II which was also evident from the fact that this discharge was associated with bile from the duodenum, which occurs during the first part of phase II. Half of the administered volume was discharged between 35 and 45 min and complete volume in 55–65 min in all cases. Total amount of the volume recovered until the end of the next phase activity was equal to or slightly less than the administered volume.

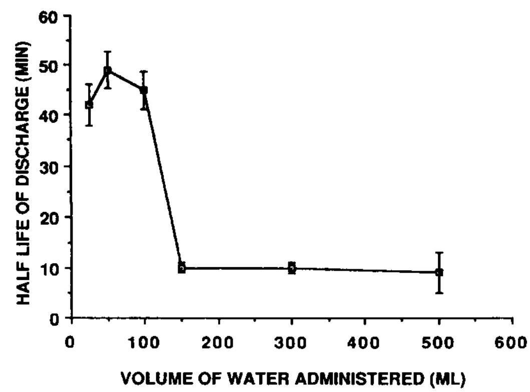

Fig. 3. Time taken for the discharge of half of the administered volume of water given 15–20 min after cessation of high antral activity, plotted against the volume of test solution. Note the change in the slope of the curve from 100 ml to 150 ml.

Mean total volume recovered during one complete cycle during which no water was administered was 28 ml.

pH of duodenal effluent

The mean pH of the duodenal discharge during one activity period without the administration of any test mean was 7.69. pH was maintained between 7 and 8 at all times following the administration of volumes up to 100 ml. However, a reduction in pH of the effluent was seen as the volumes were increased to 150 ml or more (Fig. 4). With 500 ml, a pH of as low as 1.5 was observed 45 min after the administration of test meal. The pH generally dropped 5–15 min following the administration of water and reached its lowest at different times depending on the volume administered. Range of pH for volumes upto 100 ml was 4.3 to 8.3 whereas for 150 ml and more, it was 1.5 to 8.2. Table 2 shows the pH range for different volumes of water.

Gastric emptying of liquids has been extensively reported in the literature during the last 3 decades. A variety of methods have been employed in these studies. Most of the earlier studies

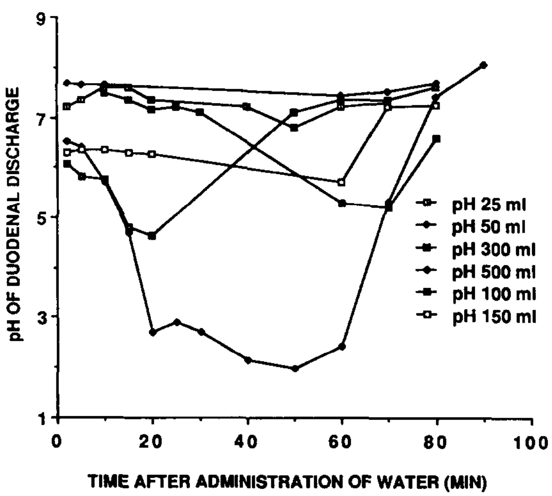

Fig. 4. pH of duodenal discharge as a function of time after administering different volumes of water (25–500 ml) 15–20 min after cessation of high antral activity in fasted dogs. The values are an average of 9 studies. S.D. bars of data were omitted for the sake of clarity. Table 2 gives an idea about the S.D. of the data.

TABLE 2

pH of duodenal effluent after administration of different volumes of water

Volume (ml)	pH Range *	
	Low	High
25	6.88 ± 0.19	7.75 ± 0.26
50	6.49 ± 1.80	7.81 ± 0.31
100	4.82 ± 1.90	7.60 ± 0.21
150	3.66 ± 0.77	7.27 ± 0.12
300	2.93 ± 0.87	7.16 ± 0.39
500	2.12 ± 0.54	8.05 ± 0.20

* Figures are the mean and S.D.

involved the administration of the test meal followed by aspiration of the volume remaining in the stomach at different time intervals using a gastric tube (Elias et al., 1968; Hunt and Knox, 1968; Weisbrodt et al., 1969). An unabsorbable and undegradable dye like Phenol red can be used in order to wash out the stomach and calculate the volume remaining from the amount of dye in the stomach (Hurwitz, 1981). Later methods involved the use of radioisotopes which could be followed by a gamma camera (Wright et al., 1981), or the use of real-time ultrasound methods to calculate the volume in the stomach (Bateman and Whittingham, 1982). Although all of the above techniques are non-invasive, they provide only an indirect estimate of fluid discharge from stomach. Also an effect on motility, and hence the discharge pattern of stomach, is obvious when aspirations are done using a gastric tube. A direct measure of fluid movement in the GI tract can only be obtained by using a cannula in the intestine or stomach. Some studies have reported the use of gastric cannula (Stemper and Cooke, 1975), but the question of its effect on the normal gastric function still remains.

The technique used in our studies involves the use of a Thomas cannula in the duodenum, about 15 cm distal from the gastroduodenal junction. While it is a direct way of measuring gastric emptying without altering gastric function, it includes the volume contribution from the bile duct, pancreatic duct and duodenal secretions. Nevertheless, this technique allows direct analysis of the fluid discharged from the stomach and monitoring parameters such as viscosity, bile content and pH of the effluent. Also all of the studies reported so far in dogs involve administration of test meals by an intragastric tube. Apart from the possibility of changing the existing motility pattern, administration by a tube will not involve receptive relaxation of the stomach, a natural phenomenon reported in the literature (Knoebel, 1982; McCoy and Bass, 1963; Cannon, 1911). Some studies (Azpiroz and Malagelada, 1985) have reported a receptive relaxation during feeding followed by a low-tone accommodation period and then a sustained high tone until return of the fasted state in dogs. Our method of administration by natural swallowing will induce the receptive relaxation in stomach and thus remove another possible artifact in such studies.

Results of the present study with volumes larger than 100 ml (hereafter referred to as large volumes) are consistent with the ones reported by Hung and MacDonald (1954). The stomach emptying of large volumes seems to follow an exponential curve with a half time of discharge in the neighborhood of 10 min. Discharge of liquid starts from the cannula immediately after administration of test meals and most of the volume is discharged within 40 min. Although some change in viscosity is observed in the effluent, there is no associated bile or mucus indicating that all the events of a fed state are not stimulated. Perhaps only the motility pattern changes temporarily and gastric secretions are induced.

The discharge pattern of 100 ml or less (hereafter referred to as small volumes) however is different from that of large volumes and has been reported for the first time. Apparently upon administration of small volumes, the existing phasic activity in the stomach i.e. phase I or the quiescent phase is not affected. Thus in the absence of any activity, the stomach is in a relaxed state and there is no pressure gradient across the gastroduodenal junction. Upon the arrival of phase II activity, most of the liquid present in the stomach is discharged into the duodenum almost as a bolus. A relationship between antral activity and liquid transit has been consistently denied in the literature (Camillarim et al., 1985; Kelly, 1980). On the other hand proximal stomach activity has been implicated in fluid discharge from the stomach (Kelly, 1980; McCoy and Bass, 1963). It follows therefore that upon administration of small volumes of liquids during phase I, no activity is induced in the stomach and consequently a coadministered dosage form will have little or no chance of distributing itself.

It is well established that addition of large volumes into the stomach leads to interruption of the interdigestive activity of the GI tract and the appearance of a characteristic fed type pattern of spike potentials and contractions. There seems to be a minimum amount of gastric content in order to change the motility pattern. Distension of the stomach by a 160 ml balloon or a 37.5–50 mm mercury pressure (Azpiroz and Malagelada, 1984; Melo et al., 1981) abolishes the fasted motor pattern in the dog. Cooke and Stemper (Stemper and Cooke, 1975; Cooke and Stemper, 1975) have reported that in dogs, a 60 ml meal did not result in a burst activity in the antrum but 120 ml or greater volume did. In the light of these findings, it appears that large volumes in our studies cause a motility pattern change from phase I to a continuous "fed-like" motility which is then responsible for the continuous and immediate discharge of liquid from the stomach. When most of the liquid is gone, activity subsides and the stomach returns to its previous activity i.e. phase I and the normal interdigestive migratory motor complex subsequently resumes. Our studies show that the volume transition to convert from a fasted to a fed state lies somewhere between 100 and 150 ml in the dog.

These two distinctly different patterns of liquid emptying from the stomach can influence the pharmacokinetics of an oral dosage form. Given with a small volume, the dosage form containing a rapidly dissolving drug may disintegrate and dissolve and then be emptied from the stomach as a bolus during phase II activity. Whereas when a large volume is given, a part of drug will dissolve in the medium and be carried into the intestine continuously over the next half an hour or so in the fasted stated. Thus for a drug which has an absorption window in the upper duodenum, a large volume may be more desirable to ensure a continuous passage of drug solution past the absorption site whereas a small volume will release the solution more or less as a bolus and may not provide sufficient time at the site of absorption. Also since gastric emptying of small volumes occurs at the onset of phasic activity, the gastric content may be cleared of the absorption window in a relatively short time, thereby reducing absorption. The fact that large volumes empty from the stomach until most of the volume is cleared and the rest of the liquid may be discharged with the next activity period. This might be a partial explanation for the double peak phenomenon observed in the plasma kinetics of certain drugs (Oberle and Amidon, 1986; Lue et al., 1986), assuming of course that enterohepatic recycling or discontinuous absorption are not involved.

pH of the duodenal effluent in dog depends on the volume of water administered. Large volumes apparently induce acid secretion in the stomach and thus lower the pH to values as low as 1.5 in the lumen of the proximal duodenum. This contradicts the view that the pH changes immediately to near-neutral once the material enters from the stomach into the duodenum. There is evidence in the literature that gastric distension (Azpiroz and Malagelada, 1984) and an increased rate of gastric emptying (Hunt, 1963) lead to an increase in gastric acid output rate. This large variability of pH suggests that dissolution and absorption characteristics of drugs with absorption predominantly from the proximal duodenum could be variable in the fasted state. The pH fluctuation could also present dissolution problems for enteric-coated tablets by delaying dissolution of their coating perhaps until the formulation is past its absorption site.

The mean resting volume in the stomach in the fasted state is about 25 ml in both dog and man (Erskine and Hunt, 1981), and administration of small volumes does not change the motility pattern. Under such conditions if a formulation is coadministered with a small volume of liquid during phase I, it may not have much opportunity to disintegrate and distribute in the stomach, given that there is also strong interaction between the particles and mucus in the stomach (Gruber et al., 1987).

In additional preliminary studies were conducted on the transit pattern of small volumes of semi-aqueous composition of test meals. 20% and 40% solutions of polyethylene glycol 400 were used. In contrast to following the motility pattern by similar volumes of water, these semi-aqueous test meals induce considerable secretions in the dog stomach and result in a continuous discharge approximated by zero-order kinetics. The pH of the effluent is also consistently low and relatively constant, at about 3.5. These data will be presented elsewhere.

It appears that the pH and transit patterns of liquids from the dog stomach in the fasted state depend on administered volume. These findings can aid the design and evaluation of sustained release dosage forms and can help fashion a more reasonable picture of the in-vivo performance of an oral dosage form.

Acknowledgements

The authors thank Dr. Peter Gruber (Dr. Karl Thomae GmbH, Bieberach, F.R.G.), Dr. Abraham Rubinstein and Mr. Vince Hon Kin Li for their useful discussions and critical comments during the course of this project.

References

Azpiroz, F. and Malagelada, J.-R., Pressure activity patterns in the canine proximal stomach: response to distension. *Am. J. Physiol.*, 247 (1984) G265–G272.

Azpiroz, F. and Malagelada, J.-R., Physiological variations in canine gastric tone measured by an electronic barostat. *Am. J. Physiol.*, 248 (1985) G229–G237.

Bateman, D.N., Effects of meal temperature and volume on the emptying of liquid from the human stomach. *J. Physiol. (Lond.)*, 331 (1982) 461–467.

Bateman, D.N. and Whittingham, T.A., Measurement of gastric emptying by real time ultrasound. *Gut*, 23 (1982) 524–527.

Camillarim, M., Malagelada, J.-R., Brown, M.L., Beker, G. and Zinsmeister, A.R., Relation between antral motility and gastric emptying of solids and liquids in humans. *Am. J. Physiol.*, 249 (1985) G580–G585.

Cannon, W.B., The nature of gastric peristalsis, *Am. J. Physiol.*, 24 (1911) 250–266.

Code, C.F. and Marlett, J.A., The interdigestive myoelectric complex of the stomach and small bowel of dogs. *J. Physiol. (Lond.)*, 246 (1975) 289–309.

Cooke, A.R. and Stemper, T.J., The function of the antrum and the pylorus in controlling emptying of liquid meals. In

G. Vantrappen (Ed.), *Proceedings of the International Symposium on GI Motility*, Typoff, Belgium, 1975, pp. 278–283.

Dressman, J.B., Comparison of canine and human gastrointestinal physiology, *Pharm Res.*, 3 (1986) 123–131.

Elias, E., Gibson, G.J., Greenwood, L.F., Hunt, J.N. and Tripp, J.H., The slowing of gastric emptying by monosaccharides and disaccharides in the test meal. *J. Physiol. (Lond.)*, 194 (1968) 316–326.

Erskine, L. and Hunt, J.N., The gastric emptying of small volumes given in quick succession, *J. Physiol. (Lond.)*, 313 (1981) 335–341.

Gill, R.C., Pilot, M.-A., Thomas, P.A., and Wingate, D.L., Organization of fasting and postprandial myoelectric activity in stomach and duodenum of conscious dogs. *Am. J. Physiol.*, 249 (1985) G655–G661.

Gruber, P., Rubinstein, A., Li, V.H.K., Bass, P. and Robinson, J.R., Gastric emptying of non-digestible solids in the fasted dog. *J. Pharm. Sci.*, 76 (1987) 117–122.

Hunt, J.N. and MacDonald, I., The influence of volume on gastric emptying. *J. Physiol. (Lond.)*, 126 (1954) 459–474.

Hunt, J.N., Gastric emptying and secretion in man. *Physiol. Rev.*, 39 (1959) 491–533.

Hunt, J.N., The duodenal regulation of gastric emptying. *Gastroenterology*, 45 (1963) 149–156.

Hunt, J.N. and Knox, M.T., A relation between the chain length of fatty acids and the slowing of gastric emptying. *J. Physiol. (Lond.)*, 194 (1968) 327–336.

Hurwitz, A., Measuring gastric volumes by dye dilution. *Gut*, 22 (1981) 85–93.

Jacoby, H.I., Bass, P. and Bennett, D.R., In vivo extraluminal contractile force transducer for gastrointestinal muscle. *J. Appl. Physiol.*, 18 (1963) 658–665.

Jian, R., Najean, Y. and Bernier, J.J., Measurement of intestinal progression of a meal and its residues in normal subjects and patients with functional diarrhoea by a dual isotope technique. *Gut*, 25 (1984) 728–731.

Kellow, J.E., Borody, T.J., Phillips, S.F., Tucker, R.L. and Haddad, A.C., Myogenic control of intestinal motility. *Gastroenterology*, 91 (1986) 386–395.

Kelly, K.A., Gastric emptying of liquids and solids: role of proximal and distal stomach. *Am. J. Physiol.*, 239 (1980) G71–G76.

Kerlin, P. and Phillips, S., Variability of motility of the ileum and jejunum in healthy humans. *Gastroenterology*, 82 (1982) 694–700.

Knoebel, L.K., Th gastrointestinal system. In Selkurt, E.E. (Ed.), *Basic Physiology for the Health Sciences*, Little, Brown and Co., Boston, 1982, pp. 469–511.

Kupfer, R.M., Heppell, M., Haggith, J.W. and Bateman, D.N., Gastric emptying and small bowel transit rate in the elderly. *J. Am. Geriatr. Soc.*, 33 (1985) 340–343.

Lind, J.F., Duthie, H.L., Schlegel, J.F. and Code, C.F., Motility of the gastric fundus. *Am. J. Physiol.*, 201 (1961) 197–202.

Lue, C.Y., Oberle, R.L., Fleisher, D. and Amidon, G.L., Application of radiotelemetric system to evaluate the performance of enteric coated and plain aspirin tablets. *J. Pharm. Sci.*, 75 (1986) 469–474.

McCoy, E.J. and Bass, P., Chronic electrical activity of gastroduodenal area: effect of food and certain catecholamines. *Am. J. Physiol.*, 205 (1963) 439–445.

Melo, J.D.C., Summers, R.W., Thompson, H.H., Wingate, D.L. and Yanda, R., Effects of intestinal secretagogues and distension on small bowel myoelectric activity in fasted and fed conscious dogs. *J. Physiol. (Lond.)*, 321 (1981) 483–494.

Miolan, J-P. and Roman, C., Discharge of efferent vagal fibers supplying gastric antrum: indirect study by nerve suture technique. *Am. J. Physiol.*, 235 (1978) G366–G373.

Nimmo W.S., Gastric emptying and drug absorption. *Pharm. Int.*, 1 (1980) 221–223.

Oberle, R.L. and Amidon, G.L., The influence of variable gastric emptying and intestinal transit rates resulting from gastrointestinal motility cycle on the plasma kinetic of cimetidine, Presented at the *18th Annual Pharmaceutical Graduate Student Research Meeting*, Chicago, University of Illinois, June 18–20, 1986.

Rees, W.D.W., Go, V.L.W. and Malagelada, J.-R., Antroduodenal motor response to solid-liquid and homogenized meals. *Gastroenterology*, 76 (1979) 1438–1442.

Reinke, D.A., Rosenbaum, A.H. and Bennett, D.R., Patterns of dog gastrointestinal contractile activity monitored in vivo with extraluminal force transducers. *Am. J. Dig. Dis.*, 12 (1967) 113–141.

Russell, J. and Bass, P., Canine gastric emptying of fiber meals: influence of meal viscosity and antroduodenal motility. *Am. J. Physiol.*, 249 (1985) G662–G667.

Stemper, T.J. and Cooke, A.R., Gastric emptying and its relationship to antral contractile activity. *Gastroenterology*, 69 (1975) 549–653.

Szurszewski, J.H., A migrating electric complex of the canine small intestine. *Am. J. Physiol.*, 217 (1969) 1757–1763.

Thomas, J.E., Mechanics and regulation of gastric emptying. *Physiol. Rev.*, 37 (1957) 453–474.

Traynor, O.J., Dozios, R.R. and DiMagno, E.P., Canine interdigestive and postprandial gallbladder motility and emptying. *Am. J. Physiol.*, 246 (1984) G426–G432.

Vantrappen, G.R., Janssens, J., Hellemans, J. and Ghoos, Y., The interdigestive motor complex of normal subjects and patients with bacterial overgrowth of the small intestine. *J. Clin. Invest.*, 59 (1977) 1027–1030.

Vantrappen, G.R., Peeters, T.L. and Janssens, J., The secretory component of the interdigestive migrating motor complex in man. *Scan. J. Gastroenterol.*, 14 (1979) 663–667.

Weisbrodt, N.W., Wiley, J.N., Overholt, B.F. and Bass, P., A relation between gastroduodenal muscle contractions and gastric emptying. *Gut*, 10 (1969) 543–548.

Weisbrodt, N.W., Motility of the Small Intestine, In Johnson, L.R. (Ed.), *Physiology of the Gastrointestinal Tract*, Raven, New York, 1981, pp. 411–443.

Welling, P.G., Effect of food on bioavailability of drugs. *Pharm. Int.*, 1 (1980) 14–17.

Wright, R.A., Thompson, D. and Syed, I., Simultaneous markers for fluid and solid gastric emptying: new variations on an old theme: concise communication. *J. Nucl. Med.*, 22 (1981) 772–776.