ELSEVIER

International Journal of Pharmaceutics 109 (1994) 91–98

international journal of pharmaceutics

Research Papers

Effect of meal viscosity on gastric pH and residual volume in the fasted dog

Pardeep K. Gupta [1], Joseph R. Robinson *

School of Pharmacy, University of Wisconsin-Madison, 425 North Charter Street, Madison WI 53706, USA

(Received 18 January 1991; Modified version received 10 December 1993; Accepted 29 December 1993)

Abstract

This study was designed to study the gastric handling of various volumes of viscous materials in dog. Based on earlier studies in which small (50 ml) or large (300 ml) volumes showed different patterns of gastric emptying, 50 or 300 ml test meals of varying viscosities were administered to fasted dogs during phase I of the motility pattern. High-viscosity grade hydroxypropylmethylcellulose was used as a viscosity inducing agent to obtain solutions with viscosities of up to 45 000 cps. Gastric residual volume was analyzed by monitoring the concentration and amount of a non-absorbable dye – phenol red in the stomach. As with meals of low viscosity, viscous fluids showed distinctly different patterns of discharge from the stomach for small and large volumes. However, for both volumes of the test meals, the rate of gastric emptying was slower compared with corresponding volumes of water (low viscosity). Small volumes of viscous meals showed longer lag periods between the ingestion of meals and the start of gastric emptying as compared with less viscous meals. 300 ml meals of viscous fluids exhibited a lag phase and linear discharge instead of the first-order discharge usually shown by comparable volumes of low viscosity. For the range of viscosities studied, there appears to be no effect of viscosity on gastric motility in the fasted state. The pH changes associated with gastric processing of viscous materials were not significantly different from those of water.

Key words: Methocel; Gastric emptying; Stomach; pH

1. Introduction

Gastric emptying of liquids has been studied and reported extensively during the last 35 years. It has been shown that gastric emptying of liquids follows first-order kinetics, the slope of the curve depending on the nature of the liquid (Hunt and McDonald, 1954). When coadministered with solids, the liquid portion empties faster and maintains a first-order kinetic discharge (Camillarim et al., 1985). However, all of these earlier studies involved large volumes of liquids, i.e., generally greater than 300 ml. Previous studies from this laboratory have shown that the pattern of gastric emptying of liquids in the fasted state is a function of the administered volume of the liquid (Gupta and Robinson, 1988; Gruber et al., 1989). During the fasted state, small volumes, generally

* Corresponding author.

[1] Present address: Philadelphia College of Pharmacy and Science, 43rd Street at Woodland Av., Philadelphia, PA 19104, U.S.A.

SSDI 0378-5173(94)00014-V

less than 100 ml, follow the phase of activity at the time of administration and empty during phases II and III only. Volumes larger than 150 ml show a different transit pattern and empty with characteristic discharge kinetics irrespective of phasic activity. This discharge pattern will fit a first-order kinetic pattern or plot of square root of volume remaining in the stomach vs time.

Gastric emptying of viscous meals has not been the subject of much attention in published studies to date. This may be due to the fact that an appropriate technique has not been available to perform such investigations. Nevertheless, the importance of such studies from a pharmaceutical perspective cannot be underestimated. A number of formulations containing swellable polymers as laxatives, or containing drugs, are available for use today. However, the rationale behind their use is only empirical.

The use of bioadhesive polymers has also been proposed as part of an effort to increase the residence time of oral dosage forms in the GI tract. Such formulations, by virtue of their mucoadhesive properties, are proposed to interact with the GI membrane mucus and be retained on the membrane for extended periods of time. These polymers are hydrophilic in nature and show variable degrees of swelling in an aqueous medium, creating highly viscous solutions or suspensions. Both swelling and bioadhesion are functions of a number of variables, including available fluid in the stomach, secretions, pH, and motility. An understanding of the gastric processing of viscous materials is therefore important to understand and optimize the performance of such systems. Most studies reported thus far on gastric emptying of viscous materials deal with solutions or suspensions of natural polymers or gums. One problem with such systems is that their rheological properties are hard to characterize. All of them are pseudoplastic in nature, and some show a thixotropic behaviour.

Most studies on viscous materials report that viscosity slows the rate of gastric emptying. However, the mechanism and extent of this change in rate of gastric emptying have been the subject of controversy. It has been proposed that the slower emptying rate of viscous meals may be the result of inhibition of gastric motility by such materials (Abrahamson, 1973; Andrews et al., 1980). Thus, a different kind of interaction of viscous material with the stomach wall is proposed. However, other studies have indicated that the slowing of gastric emptying as a result of increased meal viscosity is due to the viscosity itself rather than a change in antroduodenal motility (Russell and Bass, 1985). Using force transducers as the experimental probe, the latter authors reported that changes in motility patterns in the stomach were not different for meals of different viscosities. The materials used in such studies had a maximum viscosity of only 2000 cps. Time for discharge of half of the ingested volume ($t_{1/2}$) was reported to be 10–40 min (Russell and Bass, 1985).

Prove and Ehrlein (1982) have proposed that large volumes of a viscous material convert the canine stomach from a fasted to a fed state. This implies that the phenomenon of retropulsion is initiated after ingestion of viscous meals, resulting in retropulsion of the material back into the stomach during each contraction. This accounts for the change in gastric emptying rate for such materials. All of the studies reported to date were conducted using large volumes of test meals.

The purpose of the present investigation was to characterize the gastric processsing of meals of different viscosities in terms of rate of gastric emptying and pH change. Using viscous meals of small and large volumes, it is possible to determine their GI transit pattern and compare them to non-viscous meals such as water.

2. 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 as described below. The dogs were housed in a room with air and humidity control and 12 h light/dark cycles.

2.1. Duodenal cannula

A modified Thomas type cannula was constructed and used (Thomas, 1941; Jones, et al.,

1971). Modifications were made to extend the useful life of the cannula and to reduce the incidence of leakage and infections around the cannula. Details of the original design and the modifications made have been published earlier (Gruber et al., 1987; Rubinstein and Robinson, 1987). These modifications also expand the versatility of the canine GI system for study of pharmaceutical dosage form transit through the intestines by allowing the administration of dosage forms directly through the cannula into the duodenum.

The body of the cannula is made up of acetal (Delrin, AF-Blen, E.I. Dupont) homopolymer (Polymer Corp., Reading, PA). The cannula base is an oval-shaped flat structure with a round hole in the center. This fits inside the intestine. The stem of the cannula can be extended by adding an extension on its end which can be screwed on. The stem is threaded so that an acetal washer can be screwed on from the outside once the cannula has been inserted into the duodenum. The purpose of the washer is to anchor the cannula with the omentum and the abdominal wall of the animal. Once the incision is closed, only a few millimeters of the cannula stem are exteriorized and it is then extended by screwing onto the extension from the outside. The extension almost touches the skin to make it tight against the wound. This design significantly reduces the incidence of infections around the wound. The extension is threaded from the outside and an aluminum washer is screwed on all the way to the skin to aid in handling during operation of the cannula.

A 15 mm teflon plug is fitted snugly to the tubular opening of the cannula. The purpose of this plug is to keep the duodenal contents from dripping when the cannula is not being used. In the center of the plug length is a rubber ring with a diameter larger than the plug by 0.5 mm. This ensures that the cannula fits snugly on the inside of the stem and does not allow leakage. Flexibility of the rubber makes it easier to introduce and withdraw when in use. A stainless-steel wire (1.0 mm diameter) is screwed into the center of the plug. The length of this wire is adjusted so that when the plug is all the way in, the end of the wire is leveled with the extension. This allows for adding an aluminum cap at the end of the cannula to prevent the plug from dropping out.

2.2. Dog preparation

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 aseptic conditions. The modified Thomas cannula as described above (o.d., 21 mm; i.d., 17 mm; The University of Wisconsin Physical Plant Machine Shop, Madison, WI) was implanted in the duodenum positioning it about 15 cm from the gastroduodenal junction (pylorus). Implantation of cannula was achieved through a longitudinal cut on the side of duodenum that is 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 2 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 Angles, CA) and to accept oral administration of liquids by natural swallowing.

2.3. Administration of meals

Prior to each experiment, the dogs were fasted for 16–18 h with a free supply of water. The duodenal discharge collected from the cannula can be used to ascertain the phase of activity at any given time as described previously (Gupta and Robinson, 1988). All meals were administered during phase I with intubation at the back of the mouth of the animals. 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 cycle was awaited to time the first arrival of bile. After one complete phasic activity cycle was over, an additional 20

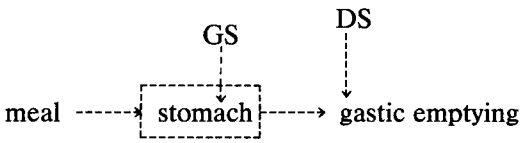
min period of no discharge was followed in order to ensure that the GI motility of the dog was in phase I. At this time, which was arbitrarily taken as time zero, the required volume of a test meal at 25°C was instilled into the back of the dog's mouth by a flexible tube (5 mm i.d.) attached to a 200 ml syringe. The dog's mouth was held up and the meal instilled at a rate of about 250 ml per min which was swallowed comfortably. Uniformity in the experimental setup with previous studies was ensured to keep the variables to a minimum and to make the comparison more meaningful.

2.4. Duodenal effluent collection

Following administration of water, all duodenal effluent was collected from the cannula at 2 min intervals for 10 min and at 5 min intervals thereafter. 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 cycle (about 120 min) and its volume and pH (Digital pH/mv meter, model 701 A, Orion Research, Cambridge, MA) determined. All studies were carried out in triplicate.

2.5. Determination of gastric volume and pH

Although the collection of entire contents from the duodenal cannula 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. Also, the resting volume of liquid in the stomach at the time of ingestion of a test meal is not accounted for in this method. In order to improve the accuracy of estimates of gastric residual volume, a new technique was developed. In this method, the test meal consists of a solution of a non-absorbable dye, which in the present study was phenol red. The duodenal effluent is then collected to obtain the total amount of dye emptied from the stomach. Simultaneously, a small sample is withdrawn from the stomach to calculate dye concentration. This gives an estimate of the dye remaining in the stomach at any time. Since no steps of addition or mixing of dye solutions are involved, this method eliminated sources of error due to these steps. By setting up a differential equation for the amount of dye remaining in the stomach at any time, it is possible to calculate the rate of gastric emptying and gastric secretions. This equation can be derived using the following model (GS, gastric secretion; DS, dye, solution):



Using the following notation: $V(0)$, residual volume in the stomach at any time zero (ml); $V(t)$, residual volume in the stomach at any time t (ml); X, rate of gastric secretion (ml/min); Y, rate of gastric emptying (ml/min); $h(0)$, amount of dye in the stomach at time zero (mg); $h(t)$, amount of dye in the stomach at any time t (mg); $C(t)$, concentration of dye in the stomach at any time (mg/ml). Then:

$$[\mathrm{d}(1/C)]/\mathrm{d}t = X/h$$

Also, the rate of gastric secretion can be calculated directly as:

$$X(t) = \{[\mathrm{d}(1/C)]/\mathrm{d}t\}\left\{h(0) - \int Y(t)C(t)\,dt\right\}$$

Since h and C are known at given time intervals, one can plot $1/C$ vs t to obtain a curve. The slope of such a curve at any point will be X/h. Also, the initial dilution of the dye gives an estimate of the resting volume of gastric contents at the time of administration of the test meal. By using this technique, gastric residual volume can be followed as a function of time.

Using this technique, gastric residual volumes were determined after water meals of 50 and 300 ml volumes. The results obtained were very close to those obtained by measuring the duodenal effluent alone as reported previously (Gupta and Robinson, 1988). This is due to the fact that the contribution from gastric secretion to the total gastric volume is very small. Therefore, in the present study, the initial dilution of phenol red was measured by drawing a gastric sample 1 min

after ingestion of the test meal. This gives the starting volume of gastric contents, which were then followed indirectly by monitoring the duodenal discharge. Subsequent gastric samples were drawn for the purpose of determining gastric pH. Phenol red was assayed by measuring the absorbance at 560 nm (Spectronic 20, Bausch and Lomb, NJ) after appropriate dilutions with 0.1 M sodium hydroxide.

2.6. Viscous solutions

High-viscosity grade hydroxypropylmethylcellulose (Methocel) was used as the viscosity inducing agent. The reason for choosing this material was due to the fact that it is non-digestible and does not have any caloric value. Using different concentrations of the material, it was possible to test a wide range of viscosities. Table 1 lists the concentrations and viscosities of Methocel solutions used in the study.

Since we now know that small and large volumes of fluids are handled differently, two volumes, representing a small and a large volume, were chosen. The small volume was chosen to be 50 ml and 300 ml was used as the large volume, since neither value is close to the critical volume of 100–150 ml for conversion from the fasted to fed state. Table 1 lists the concentrations and associated viscosities of various Methocel solutions. Since Methocel is a pseudoplastic material, the listed values of viscosities were obtained at very low shear rate (0.2 rpm, SV II sensor system). The viscosity values of Methocel solutions were relatively constant at this shear rate. A Haake RV 12 viscometer was used to measure all viscosities.

3. Results and discussion

3.1. Gastric emptying of small volumes of Methocel solutions

As shown in Fig. 1, 50 ml solutions of different concentrations of high-viscosity grade Methocel demonstrate different emptying patterns. For viscosities up to 500 cps, there is no significant difference in the gastric emptying of Methocel solutions or water.

Table 1
Various concentrations and corresponding viscosities of Methocel solutions used

Methocel concentration (% w/v)	Viscosity (cps) at 25°C
0.25	20
0.50	500
1.0	5000
2.0	45000

Gastric emptying exhibits slow emptying during the first 30–40 min and then empties as a bolus at the time which corresponds to arrival of phase II activity. Therefore, 50 ml Methocel solutions of up to 0.5% seem to follow the existing motility pattern much like water meals, when administered during phase I.

However, solutions of concentration 1.0 and 2.0% (5000 and 45 000 cps) show a different pattern of emptying. There is a well defined lag phase of about 60 min, followed by rapid emptying of the materials. Since meals of lower viscosity empty earlier (30–40 min after ingestion), this time frame does not correspond to the arrival of phase II. This increase in lag time can be due to two possibilities: (a) length of phase I (no activity phase) after ingestion is prolonged from about 35

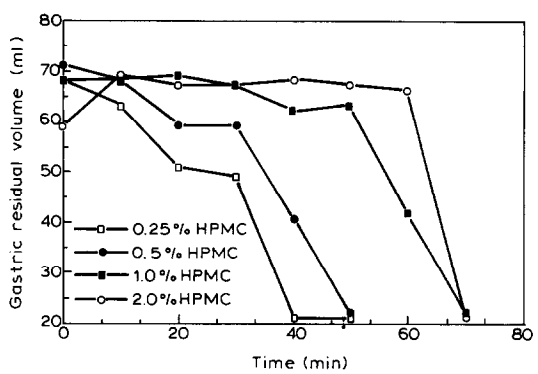


Fig. 1. Gastric emptying of 50 ml volume of liquids of varying viscosity. Gastric residual volume after administration of 50 ml of Methocel solutions of various concentrations, plotted as a function of time (viscosity values are available in Table 1). The error bars have been omitted for the sake of clarity. Typical values of standard deviations were about 15–25% of the mean.

min to about 60 min; (b) gastric emptying of Methocel solutions of 1.0% or higher does not occur during initial phase II (intermediate activity). Alternatively, perhaps activity at the beginning of phase II is not strong enough to cause the flow of viscous material. As phase II progresses towards phase III (high activity), the force of contraction increases, reaching a value at which it is able to push the material out.

From the results of studies on water (Gupta and Robinson, 1988), and data from the literature, there appears to be no support for the first possibility, i.e., phase I being prolonged. At this point, it seems more reasonable to think in terms of a greater force required to empty viscous materials. This possibility gains further ground from results of the effect of viscosity of small volumes on gastric emptying of particles of different specific gravities (Gupta, 1990). Glass particles coadministered with 50 or 300 ml of 2% Methocel solution empty rapidly about 60 min after administration. This is in contrast to the gastric emptying patterns of polystyrene and amberlite beads where the coadministered volume of Methocel solution changes the emptying pattern of particles. When coadministered with 50 ml of a 2% Methocel solution, these particles empty in the same manner as when given with water. On the other hand, when given with 300 ml of 2% Methocel solution, these particles empty with the fluid and a show a considerable degree of distribution through the GI tract. It appears to be due to the fact that glass beads, owing to their higher density, tend to settle out of the solution and empty during phase III. If the length of phase I were extended, arrival of phase III would be delayed for 50 ml of 2% Methocel solution resulting in a longer retention time for amberlite and polystyrene particles. This suggests that phase III arrives about 60 min after administration of both viscous and non-viscous meals, irrespective of the volume administered.

3.2. Gastric emptying of large volumes of Methocel solutions

Gastric emptying of a large volume (300 ml) of Methocel solution is shown in Fig. 2. Once again,

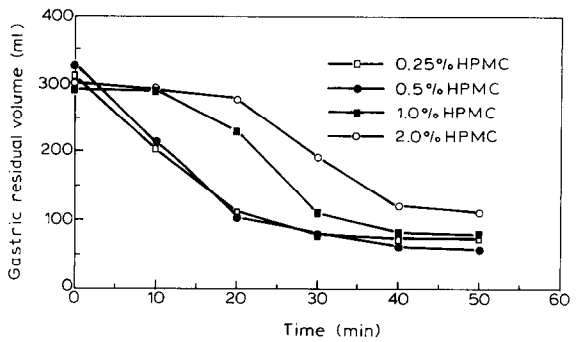


Fig. 2. Gastric emptying of 300 ml volume of liquids of varying viscosities. Gastric residual volume after administration of 300 ml of Methocel solutions of various concentrations, plotted as a function of time (viscosity values are available in Table 1). The error bars have been omitted for the sake of clarity. Typical values of standard deviations were about 15–25% of the mean.

the curves for 0.5% and lower concentrations show a distinctly different pattern from that of higher concentrations. Less viscous materials seem to empty in an exponential manner, like water, without showing any lag phase. Values of $t_{1/2}$ are 15–18 min for both the curves. However, solutions of 1.0 and 2.0% display different lag times, observed for the first time for large volumes.

There is little question about the fact that the stomach is being converted into a fed-like state once the meal has been ingested. Since the forces of contractions during the fed mode are of a similar amplitude to those in phase II of the fasted state, they may not be sufficiently strong to empty the meal. However, within 10–20 min, the contractions become progressively stronger. A true fed state seems to occur, as reported earlier (Prove and Ehrlein, 1982). This implies that the phenomenon of retropulsion may also commence which changes the emptying patterns from first to zero order. Additional studies on the effect of volume and viscosity of coadministered fluid on discharge of small particles appear to support the existence of a retropulsion phenomenon by showing that most particles are discharged along with the liquid. This would be possible only if the contents of the stomach were kept well mixed, an activity usually carried out by retropulsion.

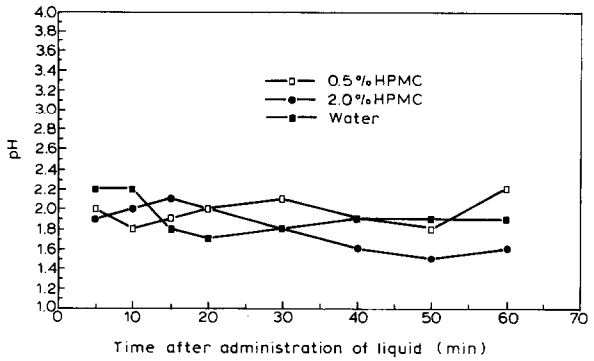


Fig. 3. Gastric pH after administration of 50 ml Methocel solutions of varying concentrations (viscosity values are available in Table 1).

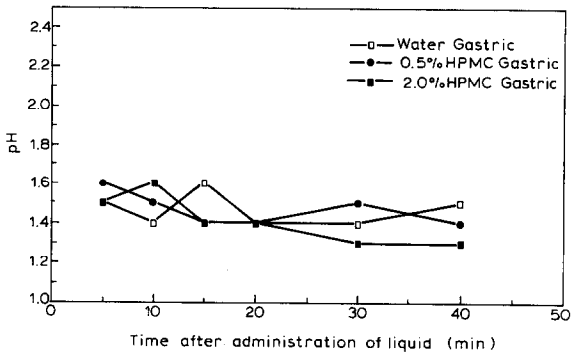


Fig. 5. Gastric pH after administration of 300 ml Methocel solutions of varying concentrations (viscosity values are available in Table 1).

3.3. Gastric and duodenal pH

As shown in Fig. 3, for small volumes, the gastric and duodenal pH values for water and various concentrations of Methocel solution are comparable. This is because none of them changes the existing motility or secretory pattern. The curve of duodenal pH for 2.0% Methocel shows a slight drop which corresponds to the longer duration of this material in the stomach (Fig. 4). During this longer residence time, perhaps it picks up extra acid from the stomach, which is not completely neutralized by bile and duodenal secretions. Gastric pH values for all solutions stay close to 2.0.

For large volumes, the gastric pH remains consistently below 2.0, as shown in Fig. 5. This is apparently due to the acid secretion induced by the large volume. However, duodenal pH values for viscous materials are lower than those for water (Fig. 6). Once again, since it takes longer for viscous materials to empty, they carry more acid from the stomach and consequently show a lower pH in the duodenum.

The resting volume in the stomach during phase I averaged about 20 ml. This volume was calculated from the degree of dilution of the non-absorbable dye in test meals. The following equation was used for this purpose;

$$V_g = V(C_m/C_a)$$
$$= V_r = V_g - V$$

where V_g is the gastric volume, V_r resting volume in the stomach, C_m concentration of dye in the

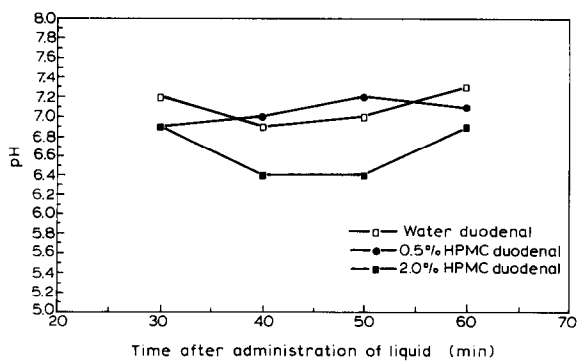


Fig. 4. Duodenal pH after administration of 50 ml Methocel solutions of varying concentrations (viscosity values are available in Table 1).

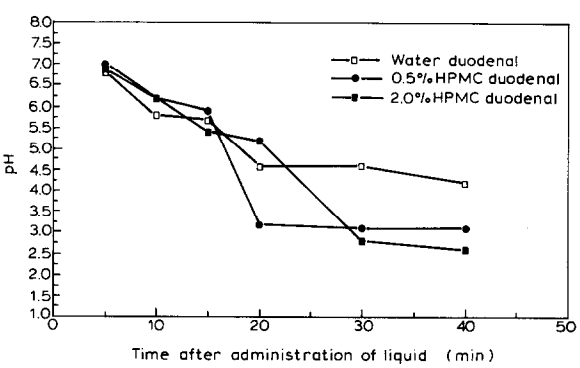


Fig. 6. Duodenal pH after administration of 300 ml Methocel solutions of varying concentrations (viscosity values are available in Table 1).

meal, C_a concentration of dye in the stomach, and V volume of meal ingested.

However, efforts to aspirate this free resting volume were not successful. Only a few mililiters in some of the studies could be aspirated. Therefore, the calculated resting volume does not seem to represent the total free fluid present in the stomach during phase I. This is not surprising due to the fact that the stomach is cleared of its contents during phase III and there is little, if any gastric secretion during phase I. Dilution of the dye could result from water that is bound to the mucin layer on the stomach mucosa. Thus, a part of the resting volume during the fasted state appears to be bound to the gastric mucin. Although, there is no report of binding of the dye to the gastric mucin or mucosa, this possibility cannot be ruled out and should be considered as a plausible explanation for the observed initial dilution of the dye concentration.

Our results are consistent with some of the previous studies reporting that viscosity slows the rate of gastric emptying. However, the question of the mechanism of the observed change in rate of gastric emptying remains unresolved. Results from the present studies appear to agree with the view that viscous materials do not change the gastric motility, and that the observed change in the rate of gastric emptying of such materials arises from their different hydrodynamics. However, in separate studies, when partially hydrated swelling polymers were administered during phase I, periods of up to 2 h were observed before gastric emptying commenced (unpublished data). This would be possible only if gastric motility were abolished or reduced with such polymers. These materials swell to yield viscosity values that are much greater than the highest viscosity used in the present investigation. It is possible that, while less viscous materials empty more slowly due to their viscosity alone, highly viscous or gel-like materials also effect gastric motility. The present study does not take into account the change in viscosity of the meal after it has been ingested. Two factors – dilution due to gastric secretions, and effect of shear produced by gastric motility – may reduce the effective viscosity of test meals.

References

Abrahamsson, H., Studies on the inhibitory nervous control of gastric motility. *Acta. Physiol. Scand.*, (Suppl. 390) (1973) 1–38.

Andrews, P.L.R., Grundy, D. and Scratchard, T., Vagal afferent discharge from mechanoreceptors in different regions of the ferret stomach. *J. Physiol.*, 298 (1980) 513–524.

Camillarim M., Malagelada, J.-R., Brown, M.L., Meder, G. and Zinsmeister, A.R., Relation between antral motility and gastric emptying of solids and liquids in humans. *Am. J. Physiol.*, 249 (1985) 6580–6585.

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

Gupta, P.K., Processing of liquids and solids by the fasted canine stomach, Ph.D. Thesis, University of Wisconsin-Madison, 1990.

Gupta P.K. and Robinson, J.R., Gastric emptying of liquids in the fasted dog. *Int. J. Pharm.*, 43 (1988) 45–52.

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

Jones, R.S., Yee, T.K. and Michielson, C.F., A modified Thomas cannula for gastric and intestinal fistulae. *J. Appl. Physiol.*, 30 (1971) 427–428.

Prove, J. and Ehrlein, H.-J., Motor function of gastric antrum and pylorus for evacuation of low and high-viscosity meals in dogs. *Gut*, 23 (1982) 150–156.

Rubinstein, A. and Robinson, J.R., Stomach and small bowel processing of theophylline products in the fasted dog, *AAPS Second National Meeting,* Boston, June 7–12, 1987.

Russell, J. and Bass, P., Canine gastric emptying of fiber meals: influence of meal viscosity and antroduodenal motility. *Am. J. Physiol.*, 249 (1985) 6662–6667.

Thomas, J.E., An improved cannula for gastric and intestinal fistula. *Proc. Soc. Biol. Med.* 46 (1941) 260–261.