

Chapter 21

Gastric Retention of Enzyme-Digestible Hydrogels in the Canine Stomach under Fasted and Fed Conditions

Preliminary Analysis Using New Analytical Techniques

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A new set of imaging techniques were used to observe the gastrointestinal transit of enzyme-digestible hydrogels in dogs. Hydrogels loaded with sodium diatrizoate/diatrizoate meglumine were detected using radiographic and fluoroscopic imaging. Swelling, propulsion, and retropropulsion of hydrogels in the stomach, as well as gastric tissue-gel interactions were monitored in real-time through the use of ultrasound imaging. Combined use of ultrasound imaging and radiographic or fluoroscopic imaging allowed us to readily locate the gel and monitor its movement. Gastric retention for 24 h under fasted conditions was achieved with hydrogels which underwent minimum deformation in response to the peristaltic wave activity. Preliminary data indicate that long term hydrogel retention in the fasted stomach can be achieved if the gel size and integrity is controlled.

Recent advances in controlled drug delivery have made it possible to deliver drugs at any desired rate for a prolonged period of time ranging from days to months (1,2). Despite such advances, the development of oral controlled dosage forms has been slow primarily due to the variability in the gastrointestinal (GI) transit time. The transit time of an oral dosage form from mouth to caecum varies from 3 h to 16 h depending on the state of the stomach (3-6). Consequently, drug concentrations in the blood may only be maintained for short and variable periods of time regardless of the controlled release properties of the device. Because of this problem, true once-a-day oral drug delivery has yet to be achieved. The primary goal in the design of oral controlled release dosage forms is to control the GI residence time of the device by overcoming the physiological barrier or barriers that contribute to the wide variation in the GI transit time. In recent years, it has generally been agreed that the gastric

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emptying time largely controls the residence time of a dosage form in the upper GI tract (7). For this reason, a great deal of interest has been focussed on controlling the gastric emptying time of the dosage form to prolong its GI residence time and improve therapeutic efficacy. Previous attempts to alter the size, shape, density, and surface properties of oral controlled dosage forms, however, had limited success in controlling the GI residence time (8-13).

Gastric motility is associated with either fed state activity or fasted state activity (14). To achieve long-term oral drug delivery, it is desirable to control the gastric residence time of the dosage form under both fed state and fasted state conditions. In the fed state, the gastric emptying of drug delivery systems will vary depending on the size of the device (3,10,12), the type of meal (3,5), and the frequency of feeding (6). In general, when the size of the device is larger than 5 mm in diameter, it will be retained in the stomach until the digestive contents of the stomach are emptied (12,15-17). The gastric residence time of the device is likely to be shortest in the presence of an acaloric liquid instillate and longest in the presence of a highly caloric solid meal (3,5,18-20). Although there is still debate regarding the mechanism of solid-liquid partitioning in the stomach (21,22), gastric retention of a dosage form for 12-16 h may be achieved with the frequent administration of food (6); however, this approach may be impractical from a patient compliance standpoint.

In the fasted state, GI motility is characterized by a cyclically recurring, 4-phase myoelectric complex known as the interdigestive myoelectric motor complex (IMMC) (23,24). The gastric retention time of many nondigestible materials is largely controlled by phase III of the IMMC (20). In the canine stomach, phase III activity occurs when 100% of the pacesetter potentials originating in the greater curvature of the orad corpus (25) are accompanied by action potentials corresponding to peristaltic contractions (26). Under maintained fasted conditions, phase III activity occurs approximately every 100 min. Phase III activity can be immediately abolished by the administration of liquids or solids and will remain absent depending on the quantity and caloric value of the food. The duration of absence, however, is more likely dependent on the physicochemical properties of the ingesta (23,27). When phase III activity resumes, it invariably begins distal to the stomach. Because of its recurring property and high propulsive efficiency, phase III of the IMMC is the most crucial physiological barrier in the GI tract that must be overcome in order to control and prolong the GI residence of drug delivery systems.

To control the gastric residence time of the dosage forms in the fasted state, we need to identify factors important to gastric retention. Identification of such factors requires visualization of the behavior of dosage forms in the stomach. Of the many imaging techniques used in humans, gamma scintigraphy has become used widely to estimate the gastric emptying time of solid and liquid materials. In animals, the gastric emptying time is commonly estimated using gamma scintigraphy, radiography, or duodenal cannulation. These techniques, however, are self-limiting in that the response of the object of interest to dynamic events occurring in the stomach is difficult to visualize in real-time. The properties of the dosage form which are critical to gastric retention during fasted state activity can be more accurately assessed by visualizing the interactions between the dosage form and the gastric tissue undergoing

peristalsis. Recently, enzyme-digestible hydrogels were developed as platforms for long-term oral drug delivery systems (28,29). These systems were studied in the canine stomach using ultrasound imaging (30). Ultrasound imaging provided real-time visualization of propulsion, retropulsion, and swelling of hydrogels in the stomach. More importantly, it was used to examine gastric tissue-gel interactions under varying gastric conditions. Ultrasound imaging, however, became difficult as more fluid emptied from the stomach. This was due to the attenuation of sound arising from gaseous particles in the lumen. Consequently, we combined ultrasound imaging with radiographic or fluoroscopic imaging. Using both imaging techniques, we were able to clearly observe the dynamic responses of an enzyme-digestible hydrogel in the fasted and fed stomach of a dog.

Our previous study in the fed state suggested that gastric retention would result when the propulsive efficiency of peristaltic contractions is minimized (30). In that study, the gastric retention of cylindrically shaped hydrogels (16 mm in length x 14 mm in diameter in the partially swollen state) was controlled by varying the degree of gastric distention using water. As the degree of gastric distention increased via repetitive administrations of water, neither the orad (retropulsive) nor the caudad (propulsive) movements of the gel were affected much by peristaltic contractions moving through the stomach. The degree of gastric tissue-gel interactions during peristalsis and thus the propulsive efficiency of peristaltic contractions was inversely related to the degree of gastric distention. Under maintained gastric distention, the gel primarily resided in the body of the stomach. As the degree of gastric distention was reduced due to the emptying of water, both the orad and caudad movements of the hydrogel were affected by peristaltic contractions moving through the stomach. Because of the intimate contacts between gastric tissues and hydrogel, the gel moved into the pyloric antrum. After all the water had emptied from the stomach, gel emptying resulted. This observation suggests that minimizing the propulsive efficiency of peristaltic contractions results in gastric retention. Minimizing the propulsive efficiency of peristaltic contractions in the fasted state may be achieved by manipulating the properties of the hydrogel. Therefore, we varied the hydrogel properties and examined how a hydrogel could be retained in the stomach under fasted conditions.

Materials and Methods

Albumin-crosslinked polyvinylpyrrolidone (PVP) hydrogels were prepared by free radical polymerization using 1-vinyl-2-pyrrolidinone (Aldrich) as a monomer, functionalized albumin (FA) as a crosslinking agent, and 2,2-azobis(2-methylpropionitrile) (Eastman Kodak) (28). The monomer solution was degassed and purged with nitrogen followed by polymerization at 60°C for 18 h under nitrogen. Once polymerization was complete, the gels were removed and cut into cylinders. The prepared gels were purified and dried as described previously (29). The dried gels were then allowed to swell in a 4% (v/v) solution of diatrizoate meglumine/sodium diatrizoate (Gastrografin (GG), Squibb Diagnostics) for 32 h at 37°C. The GG-loaded gels were air dried for one week and later oven dried at 37°C

for at least one week. Before each animal study, the dimension and weight of each dried gel were recorded. Under the present loading conditions, one gram of dried gel retained approximately 0.38 g of GG. Just prior to administration of the gel to a dog, the dried hydrogel was partially swollen in a 4% (v/v) GG solution for 15 min to impart lubricity on the gel surface to ensure safe transit to the stomach.

Imaging Technique. Standard lateral and ventrodorsal radiographs of the abdomen were made using a 1200 Ma, 150 KVP x-ray generator (General Electric Corporation, Milwaukee, WI). The animal was positioned in right lateral and dorsal recumbency. The same radiographic technique (76 & 86 KVP, 12 MaS), x-ray cassettes, film and film processing were used so that the decreasing opacity of the hydrogel could be monitored. Fluoroscopy was accomplished with the animal in sternal recumbancy. This allowed the hydrogel to be positioned in the body and/or pyloric antrum so that observations of the hydrogel movements could be made and recorded on video tape.

The ultrasound examination of the stomach was performed with a real time mechanical sector scanner (Interspec, Conshohocken, PA) using a 5 mHz transducer. After clipping the hair on the ventral right side of the body just caudal to the costal arch, copious amounts of an ultrasound transmission gel (Lafayette Pharmacal Inc., Lafayette, IN) was applied to the skin. With the animal in a standing position, a transverse view of the cranial abdomen (sagittal view of the stomach) was obtained. The gastric tissue-gel interactions were observed and recorded on video tape. With a sagittal view of the hydrogel frozen on the monitor, the image of the gel was measured and recorded on a video format camera.

Animal Experiments. A healthy mongrel dog weighing 35 lb was used throughout the study. Before each experiment, the animal was fasted for at least 15 h and then radiographed just before the administration of a gel to ensure the absence of food in the stomach. For each experiment, 380 ml of water was instilled just before the administration of a gel. An additional 380 ml of water was given at every 30 min for up to 3 h when more exposure of the gel to water was desirable. Water was instilled using a stomach tube and syringe. To maintain fasted state conditions, no food or water was given to the animal after the last administration of water. Hydrogel integrity was varied by controlling the size of the glassy core in gels which achieved the same approximate dimensions after swelling. This was accomplished by using hydrogels with different dimensions in the dried state and by controlling hydrogel exposure time to water in the stomach. The initial size of the gel was varied from 18 mm in length by 26 mm in diameter to 29 mm in length by 29 mm in diameter. Smaller sized gels swelled to a completely amorphous network in about 4 h. Larger sized gels, however, contained a glassy core and an amorphous outer layer which could be assessed through ultrasound imaging.

Over the course of these experiments, if gastric retention in the fasted state was observed for 24 h, the animal was given a standard pelletized meal once-a-day. The purpose for this was to observe the effects of food on hydrogel retention and also to determine if the presence of the gel had any effect on inhibiting the transit of food.

Results.

Gastric retention of hydrogels with a partially swollen size of 18 mm in length by 26 mm in diameter was examined. After 2.5 h in the stomach, the gel increased in size to 29 mm in length by 33 mm in diameter. When the stomach lumen was largely distended, the hydrogel resided in the pyloric antrum where gel retropulsion was observed during peristaltic contractions. After 4 h, ultrasound detected that the gel was completely amorphous and that most of the water had emptied from the stomach. When a peristaltic contraction moved through the pyloric antrum, hydrogel deformation in response to a contraction was quite pronounced as seen through fluoroscopy. When a peristaltic contraction made initial contact with the hydrogel, the gel became compacted and partially deformed against the pyloric sphincter. As the contraction migrated along the gel's surface, the left half of the gel was compressed into the antrum while the right half was still compacted against the pyloric sphincter (Figure 1). The gel was subsequently retropelled once the contraction reached the distal end of the hydrogel. Fluoroscopic images taken after 5 h located the gel in the small intestine where the gel passed quite rapidly with fluid-like characteristics.

In another study, hydrogels with a partially swollen size of 29 mm in length by 29 mm in diameter were used. After 2.5 h in the stomach, a gel diameter of 36 mm was achieved. Ultrasound imaging at 3.5 h showed an acoustic shadow which was largely attributed to the glassy polymeric core. The presence of a glassy core had a profound influence on the gastric retention time. Once most of the fluids had emptied (approximately 4 h after gel administration), the gel resided in the pyloric antrum. When a peristaltic wave moved through the pyloric antrum, hydrogel deformation in response to contractions was limited to the amorphous edges of the hydrogel. When a peristaltic contraction made initial contact with the hydrogel, the gel became compacted against the pyloric sphincter. As the wave migrated axially toward the most distal region of the gel, deformation occurred only at the gel edge (arrow in Figure 2) before retropulsion. Over the first 24 h, under fasted conditions, the peristaltic contractions were ineffective in deforming the gel and propelling it through the pyloric sphincter. Thus, it appeared that minimizing gel deformation in response to peristaltic contractions resulted in gastric retention of the gel. Comparison with our previous study (30) suggests that both the gel size and the gel integrity are two parameters critical to hydrogel retention under fasted conditions. Once the water had emptied from the stomach, gel swelling is expected to be limited since the amount of gastric fluid under fasted conditions is not significant. Once the water had emptied from the stomach, however, assessment of the glassy core with ultrasound was no longer effective due to the attenuation of sound by gaseous particles in the partially occluded lumen. In this case, fluoroscopic imaging was used to indirectly monitor the presence of the glassy core by assessing gel deformation in response to peristaltic contractions. During the 24 h-fasted conditions, gel deformation in response to peristaltic contractions gradually increased. The deformation, however, was only slightly greater than that observed in Figure 2.



Figure 1. Fluoroscopic image illustrating maximum gel deformation in response to a single peristaltic contraction. When the peristaltic contraction passes over the gel, it becomes flattened (arrows) and subsequently retropelled. The image was taken 4 h after the administration of the gel.



Figure 2. Fluoroscopic image illustrating minimum gel deformation in response to a single peristaltic contraction. When the peristaltic contraction passes over the gel, the deformation was limited to the edges of the gel (arrow). The image was taken 12 h after the administration of the gel.

On radiographic images taken 24 h after gel administration, noticeable traces of GG in the animal's colon were detected as indicated by arrowheads in Figure 3. It should be noted that the diffusional loss of GG from the gel was not significant. In vitro radiographic images made of a GG-loaded hydrogel in the simulated gastric fluid showed that the loss of GG from the gel was insignificant. This indicates that the release of GG under fasted conditions (Figure 3) was due to a mechanism other than simple diffusion. Over the 24 h of gastric retention of the gel, degradation on the gel surface became apparent as indicated by arrowheads in Figure 4. This suggests that the surface of the gel was attrited by the repeated contacts between the gel and the gastric tissue undergoing peristaltic contractions. Thus, it appears that surface erosion of the hydrogel was responsible for the release of GG from the gel. After the gel was retained in the stomach for 24 h under fasted conditions, the animal was given a standard pelleted meal at 24 h and 48 h. In the presence of food, the size of the gel reduced significantly. Figure 5 shows a gradual decrease in the hydrogel size over a period of 60 h. The size of the gel decreased much faster in the presence of food than in the fasted state. Food in the stomach apparently accelerated the surface erosion of the gel. The presence of the gel had no apparent effect on the emptying of food. Radiographic images made at 72 h illustrated that the hydrogel was neither in the stomach nor the intestines. This observation suggested that the presence of surface erosion combined with the effects of gel swelling and bulk degradation led to hydrogel disruption in the stomach.

Discussion

Our study indicated that the presence of a glassy core had a profound influence on gastric retention of hydrogels in the fasted state. When hydrogel deformation was minimal in response to gastric contractions, the contractions were ineffective in propelling the gel through the pyloric sphincter. It was this limited deformation in response to peristaltic activity that contributed to gastric retention. Although the hydrogels used in this study did not have exactly the same dimensions after the last instillation of water, their contrasting physical properties served as a useful comparison in understanding the effects of gel integrity on gastric retention. Integrity alone, however, does not guarantee hydrogel retention. In our previous studies, gels (16 mm in length by 14 mm in diameter) with only a moderate degree of swelling, emptied from the stomach within 2 h (30). The gel emptied from the stomach even though its deformation in response to gastric contractions was not significant. Thus, the size of the gel must also contribute to gastric retention. A third parameter that may influence gastric retention, under fasted conditions, is the gel's surface properties. The "slippery" surface of the gel arising from hydration and surface erosion appeared to facilitate both the movements of contractions along the gel surface and hydrogel repulsion. Since only one type of hydrogel made of PVP was used in this study, the effects of gel surface properties on gastric retention requires further investigation. The important point here is that long-term gastric retention was achieved in the fasted state and was largely attributed to the combined effects of size,

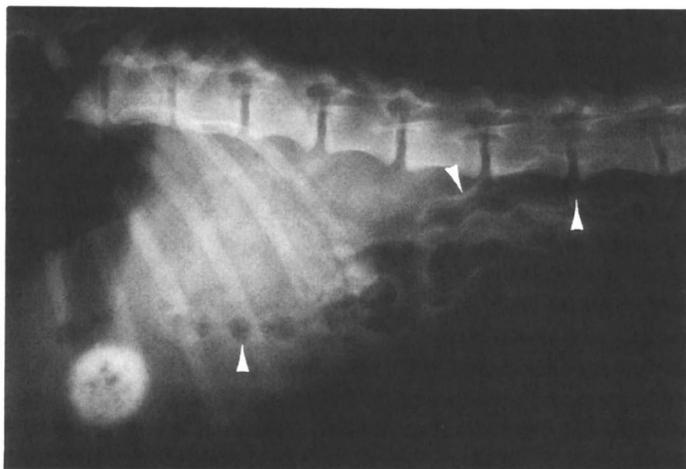


Figure 3. Lateral radiograph of the abdomen made at 24 h following administration of a GG-loaded gel. The presence of GG in the colon is indicated by arrowheads.

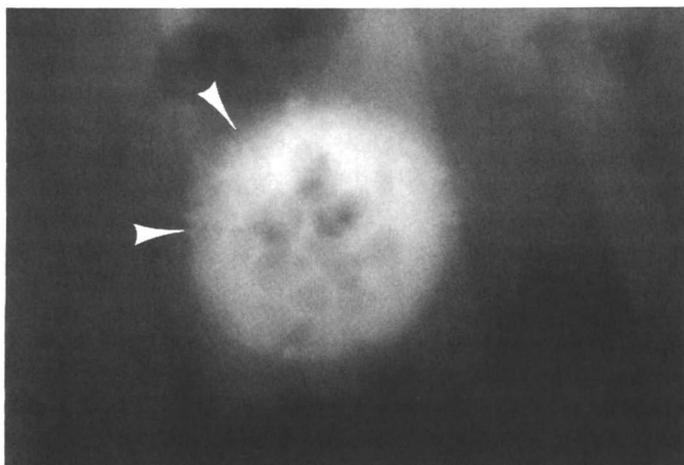


Figure 4. Close-up view of the GG-loaded gel in the pyloric antrum of the stomach. Surface erosion is indicated by arrowheads.

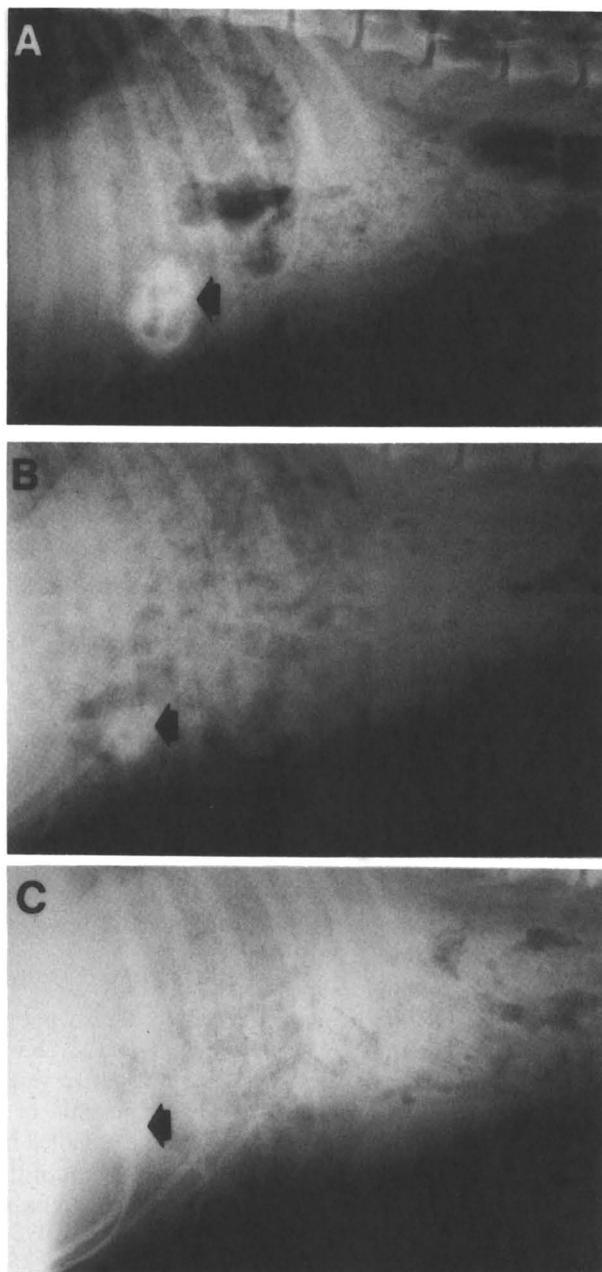


Figure 5. Lateral radiographs of the abdomen made at 36 h (A), 48 h (B), and 60 h (C). The size of a hydrogel (arrow) gradually reduced in the presence of food mainly due to the surface erosion.

integrity, and possibly surface lubricity. These effects served to minimize the propulsive efficiency of peristaltic contractions.

The surface erosion of gels in the stomach may be utilized as an effective means to deliver drugs to the body for extended periods of time. If we consider the GG to be a model drug, it is conceivable that sustained drug release can be achieved by a combination of erosion-controlled and diffusion-controlled release mechanisms. Although a more detailed analysis of drug release will be examined in future work, the preliminary findings from this study look quite promising with respect to once-a-day or even once-a-week drug delivery.

Even though the hydrogels used in this study may be useful in some veterinary applications (31), they are not yet ready for human studies since the initial size of the device is rather large for swallowing. The data collected in this present study, however, will be vital to the design of a new system which is more suitable for swallowing. Long-term gastric retention of hydrogels may be achieved by utilizing a biodegradable system that contains an inner core of high integrity for the minimum gel deformation and an outer core of high swelling capacity for the large gel size. This new design would be based on a 2-phase hydrogel network that contains a highly crosslinked, moderately swelling polymer as the inner phase and a loosely crosslinked, highly swellable polymer as the outer phase. In the stomach, this device would produce a size and integrity comparable to the present design, but its initial size would be small enough for easy swallowing.

In human studies, gamma scintigraphy has been used to study the GI transit of both digestible and nondigestible material because it is noninvasive and exposes the individual to only low radiation doses. One disadvantage of this approach is that the transit of only the labelled material can be monitored over time. When the contents of the stomach consist of nonlabelled digestible material and a labelled, nondigestible dosage form, this technique provides very little information regarding the gastric emptying of the dosage form relative to the digestible material (10). Furthermore, the gastric tissue-dosage form interactions during coordinated contractile events cannot be visualized. Thus, gamma scintigraphy does not provide a true understanding on the dosage form properties which are critical to controlling gastric retention. Consequently, when the drug delivery system is hydrophilic, ultrasound imaging may be utilized to study gastric retention in humans more accurately.

Hydrogels have received tremendous interest for their wide range of drug delivery applications (1). In particular, bioadhesive hydrogels (32) and pH-dependent swelling hydrogels (33) have been developed for oral drug delivery. Even though a great deal of research has been done to show the excellent potential of these systems in vitro, in vivo performance has either been untested or quite limited in success. As a result, in vivo studies are critical to the further development of these systems. Because ultrasound imaging can monitor hydrogel swelling and gastric tissue-gel interactions in real-time, the utilization of hydrogels as oral drug delivery devices can be better assessed. Although there are some limitations with the ultrasound imaging technique such as poor resolution depending on the amount of subcutaneous fat and individual anatomical variations (34), this imaging technique warrants further

consideration as a tool for the study and the rational design of long-term oral drug delivery systems.

In summary, the advantages of our approach to studying gastric retention are twofold. First, hydrogel response to the gastric environment can be noninvasively visualized in real-time. Second, a more efficient and justifiable approach to the development of long-term oral drug delivery systems can be achieved.

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