# Use of ultrasound imaging and fluoroscopic imaging to study gastric retention of enzyme-digestible hydrogels

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Ultrasound and fluoroscopic imaging techniques were used to monitor the gastric retention of enzyme-digestible hydrogels in the canine stomach. When water was present in the stomach, ultrasound imaging was very effective in monitoring the position of the hydrogel in the stomach, solvent penetration into the gel, and the gastric tissue–gel interactions during peristalsis. Rubbery or fully swollen hydrogels appeared as sonolucent objects with ultrasound imaging. Partially swollen hydrogels displayed a sonolucent outer layer due to solvent penetration and a centrally located bright echo resulting from the acoustic impedance mismatch at the glassy/rubbery interface. The degree of gastric tissue–gel interactions during peristalsis was inversely related to the extent of lumenal distention with water. The effectiveness of peristaltic contractions in driving the hydrogel toward the pyloric sphincter increased as the water was emptied from the stomach. In the absence of water, imaging of the gel with ultrasound became difficult. For this reason, gels were loaded with diatrizoate meglumine/sodium diatrizoate to visualize in real-time using fluoroscopic imaging. Fluoroscopic imaging allowed only indirect assessment of the hydrogel movement during peristalsis and the degree of hydrogel swelling. The gastric retention of the hydrogel under fasted conditions was influenced by the degree of gel deformation in response to peristaltic contractions. Hydrogels with a low degree of deformation during peristalsis showed long gastric retention times. The utilization of ultrasound imaging and fluoroscopic imaging for monitoring dynamic events in the stomach provided information on hydrogel properties which are important to gastric retention. The use of these imaging techniques in the development of long-term oral drug delivery systems is described.

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In the design of sustained release oral drug delivery systems, controlling and prolonging the gastrointestinal (GI) residence time of the device is important to minimizing fluctuations in the duration and extent of drug absorption[1–6]. The gastric emptying time of the device quite often controls its GI residence time between the mouth and the caecum[5, 7–11]. Thus, the oral bioavailability of the drug can vary due to differences in the gastric emptying time of the dosage form. Identifying the properties of a device that control gastric emptying is critical in developing once-a-day or once-a-week oral dosage forms. Usually, the gastric emptying time is used as a primary parameter to assess the ability of a dosage form to be retained or emptied from the stomach. Gastric emptying of potential drug delivery systems has been monitored using radiography[10, 12–15], $\gamma$-scintigraphy[2, 3, 5, 6, 16–18], radiotelemetry[8, 11, 19], and duodenal cannulation[9, 20, 21]. Alterations in the size[4, 10, 14, 17, 20–22], shape[14, 21, 22], integrity[13], density[20, 21, 23, 24], and surface properties[16, 25, 26] of the device have had limited success in controlling the gastric emptying time or gastrointestinal transit time. Evaluation of specific properties of a device based solely on the gastric emptying time may be misleading since the dynamic events in the stomach that affect the gastric residence time of the device are not directly examined. Visualizing how a device in the stomach responds to dynamic events such as gastric motility may provide the information necessary to control the gastric emptying time of the device. Recently, enzyme-digestible swelling hydrogels have been developed as platforms for long-term oral drug delivery[27, 28]. Hydrogel responses to the dynamic events in the stomach have been visualized in real-time using ultrasound and fluoroscopic imaging techniques. Here, we describe the application of these imaging techniques for monitoring the gastric retention of enzyme-digestible hydrogels in the canine stomach.

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## MATERIALS AND METHODS

### Hydrogel preparation

Human serum albumin was functionalized as previously described[27, 28]. Albumin-crosslinked polyvinylpyrrolidone hydrogels were prepared by free radical polymerization at 60°C under nitrogen using 1-vinyl-2-pyrrolidinone (Aldrich) as the monomer, 2,2-azobis(2-methylpropionitrile) (Eastman Kodak Co.) as the initiator, and functionalized albumin (FA) as the crosslinking agent. Synthesized hydrogels were washed over a three day period with distilled deionized water. The gels were then dried at room temperature for one week and then at 37°C for an additional week. Dried gels were allowed to swell in a 4% (v/v) solution of Gastrografin (GG, diatrizoate meglumine/sodium diatrizoate, Squibb Diagnostics) for 32 h at 37°C. GG was loaded to make the gels radiopaque. The gels were then air dried for one week and oven dried at 37°C for at least one week.

### Imaging techniques

Since the objective of our study was to show that ultrasound and fluoroscopic imaging techniques could be used to study the hydrogel retention in the stomach, one healthy mongrel dog weighing 16 kg was used throughout the study. In each experiment, the animal was fasted for at least 18 h and a radiograph was made to ensure the absence of food in the stomach. The ultrasound examination of the stomach was performed with a real-time mechanical sector scanner (Interspec) 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.) 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. Fluoroscopic images of the stomach were obtained using a 1200 Ma, 150 KVP X-ray generator (General Electric Corporation). 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.

### Animal experiments

Dynamic motions of the hydrogel in response to the gastric motility were studied in the presence of water and under fasted conditions using gels with different sizes and integrity. In each experiment, 380 ml of water was instilled using a gastroesophageal tube and syringe just prior to administering the hydrogel. This was intended to facilitate hydrogel swelling in the stomach. An additional 380 ml of water was administered every 30 min for up to 3 h to vary the degree of hydrogel swelling (see below). Once the instilled water had emptied from the stomach, fasted conditions were maintained for 24 h. The size of the swollen hydrogel in the stomach was varied using gels synthesized in different sizes. The integrity of the hydrogel was varied by using fully swollen or partially swollen hydrogels. The contrast in physical properties was achieved by using hydrogels with different dimensions in the dried state and by altering the gel's exposure time to water following gel administration. After the administered water had emptied from the stomach, the smaller dried gels (2.3 cm diameter; 1.6 cm length) became fully swollen with a rubbery network in about 4 h. Larger dried gels (2.7 cm diameter; 2.7 cm length), however, were only partially swollen after the water had emptied from the stomach and thus consisted of a glassy core and a rubbery outer layer. The glassy core was visualized using ultrasound imaging when water was present in the stomach. In the absence of water, the glassy core was indirectly assessed with fluoroscopic imaging. The overall dimensions of the fully swollen and partially swollen hydrogels were maintained the same.

## RESULTS

### Ultrasound imaging

The images of the hydrogel in the stomach, gel movements in the stomach, and gastric tissue-gel interactions were readily monitored in real-time using ultrasound imaging. A fully swollen hydrogel (1.0 cm diameter; 1.2 cm length) in the stomach appeared as a sonolucent object (the black object shown between the white arrowheads in *Figure 1*). When the lumen of the stomach was largely distended with water, the gel resided in the body of the stomach. As the peristaltic contractions migrated toward the distal stomach, the gastric tissue (black arrows in *Figure 2*) made very little contact with the hydrogel (white arrows in *Figure 2*). The peristaltic migration from left to right in *Figure 2* represents the movement of the gastric contraction toward the distal stomach. Because of the limited degree of gastric tissue-gel interactions, the peristaltic contractions were ineffective in driving or propelling the hydrogel toward the pyloric antrum. Gastric tissue-gel interactions, however, were enhanced as more water emptied from the stomach. When the

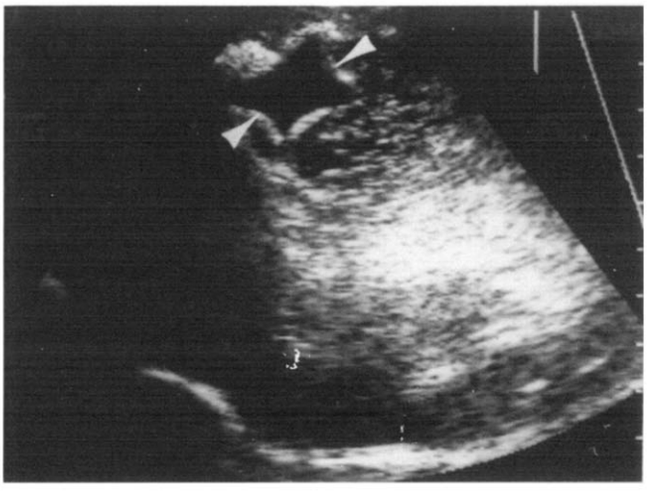

**Figure 1** The sagittal view of the stomach by ultrasound imaging. The sonolucent hydrogel is shown in the near field. The edges of the hydrogel are indicated by the white arrowheads.

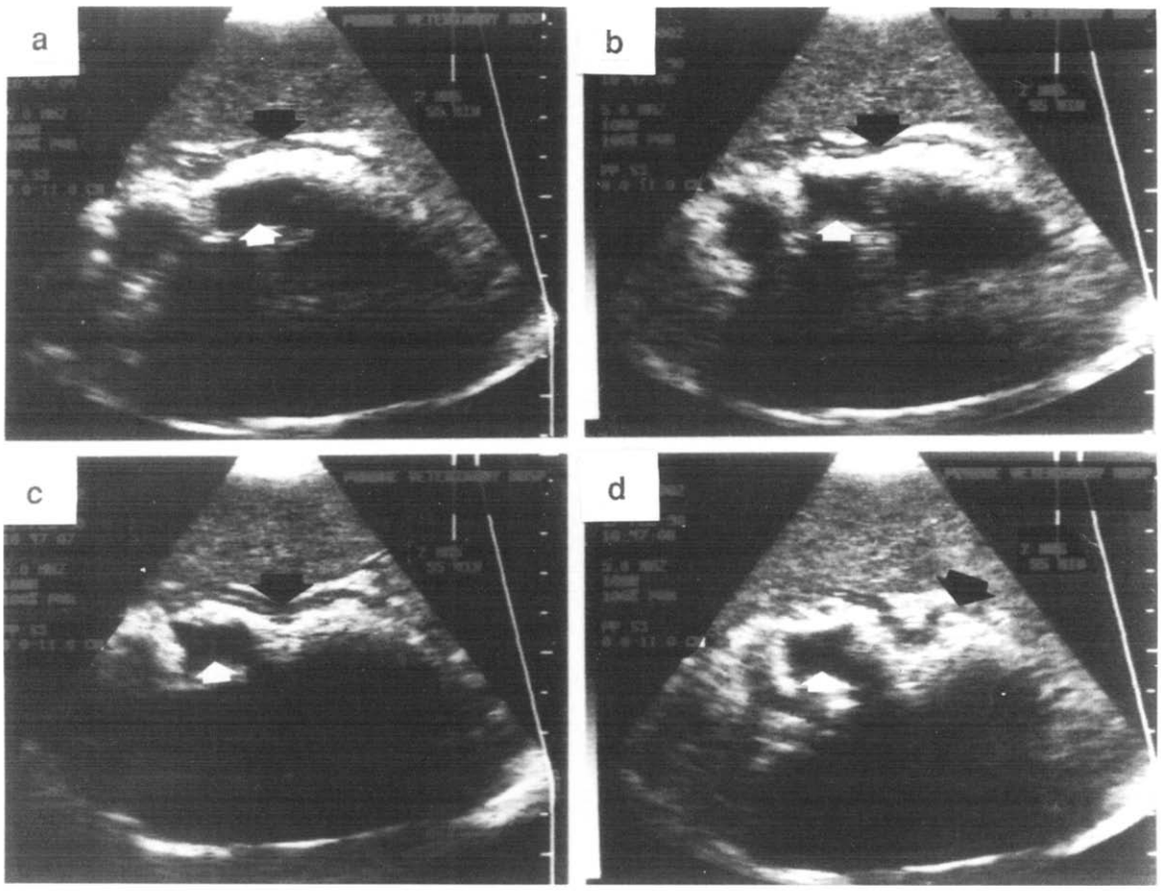


**Figure 2** Sagittal ultrasound images of a largely distended stomach were made over a period of 4 sec (**a-d**). The excursion of the sonolucent stomach wall (black arrows) can be observed adjacent to the sonolucent hydrogel (white arrows). Note that as the peristaltic wave passes through the body of the stomach, there is very little interaction between the gastric tissue and the gel. This phenomenon was only observed when the stomach was largely distended.

lumen of the stomach was only moderately distended, the peristaltic contractions propelled the hydrogel from the body of the stomach to the pyloric antrum. Ultrasound images of the pyloric antrum region (*Figure 3*) showed that the hydrogel was retropelled (retrograde movement) toward the body of the stomach following the aboral migration of the peristaltic contraction through the pyloric antrum. The gastric tissue undergoing peristalsis made an initial contact with the hydrogel as illustrated in *Figure 3a*. *Figures 3b* and *3c* show the peristaltic contraction migrating along the surface of the hydrogel. Retropulsion resulted when the contractile wave reached the distal region of the gel (*Figure 3d*). The peristaltic migration from the lower left corner to the upper right corner of *Figure 3* represents the movement of the gastric contraction from the pyloric antrum toward the pyloric sphincter. The nature of the gastric tissue–gel interactions during peristalsis as visualized through ultrasound is schematically illustrated in *Figure 4*. It should be noted that the contacts made between the hydrogel and the gastric tissue were greater since the stomach lumen was less distended. *Figure 5* shows the interaction between the gastric tissues and the hydrogel when most of the water had emptied from the stomach. One end of the hydrogel (between black arrows in *Figure 5*) was aligned with the pyloric sphincter (between white arrowheads in *Figure 5*). Because of the absence of water in the stomach, the migrating peristaltic contractions were capable of driving the hydrogel through the pyloric sphincter and into the duodenum. It should be noted that as more water emptied from the stomach, the echogenic properties of gaseous particles in the lumen made it increasingly more difficult to image the hydrogel with ultrasound.

When a large volume of fluid was retained in the stomach with the additional instillation of water, solvent penetration into fully swollen (2.3 cm diameter; 1.6 cm length) and partially swollen (2.7 cm diameter; 2.7 cm length) hydrogels could be monitored over time. In *Figure 6*, the image of the partially swollen hydrogel depicts the rubbery outer layer of the gel as the sonolucent region (black area represented by *r* in *Figure 6*) and the glassy/rubbery interface as the bright echo just proximal to the sonolucent region (white area marked by the arrow in *Figure 6*). Since the transmission of sound waves was blocked at the glassy/rubbery interface, an acoustic shadow developed in the far field of the image (black region represented by *s* in *Figure 6*). The degree of solvent penetration into the hydrogel was monitored over time by measuring the distance between the outer surface of the gel and the glassy/rubbery interface. *Figure 6* shows that the degree of solvent penetration into the gel can be quantified by measuring the increase in the thickness of region *r*. For the partially swollen hydrogel, the thickness of the rubbery outer layer increased from approximately 0.1 cm after 0.5 h

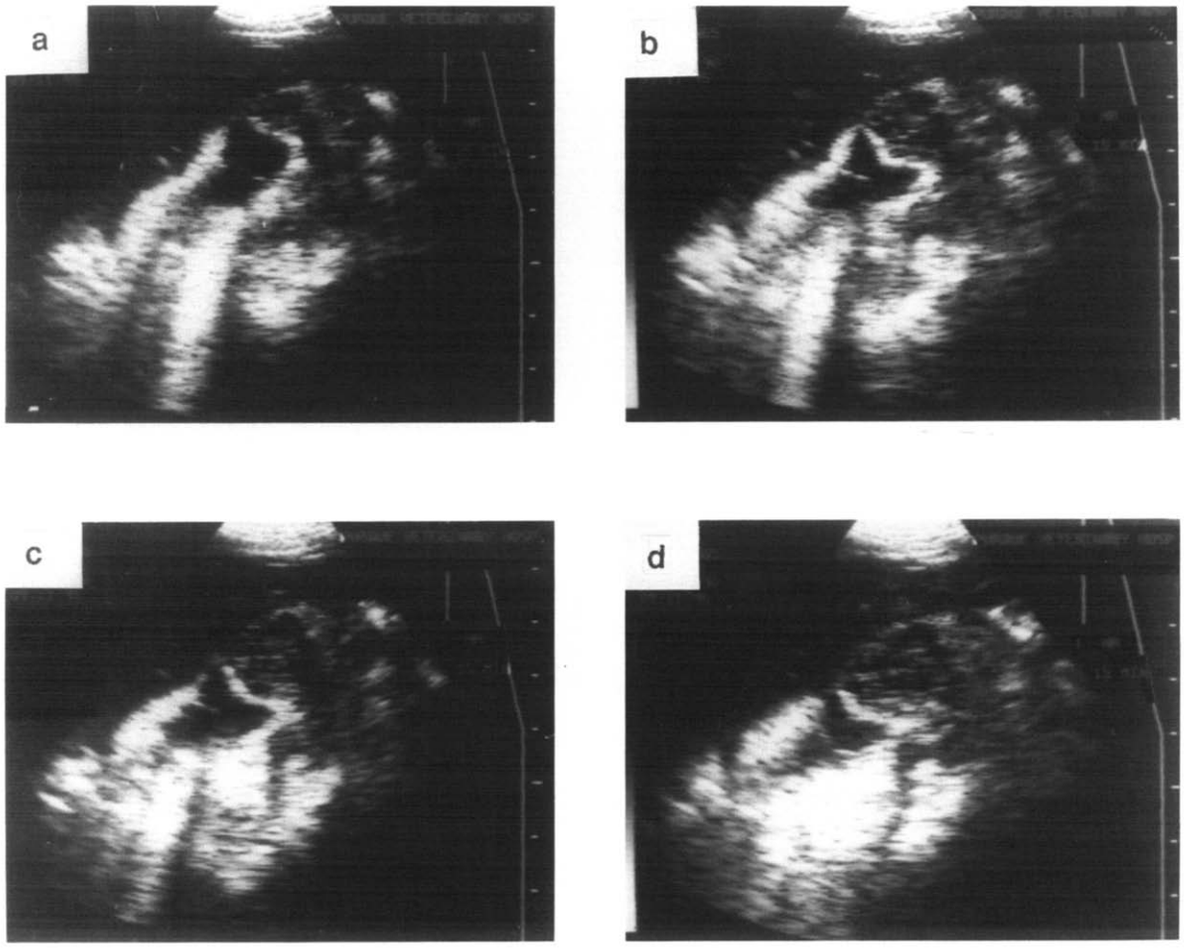


**Figure 3** Sagittal ultrasound images of a moderately distended stomach were made over a period of 1 sec (**a-d**). Note that as the peristaltic wave passes through the pyloric antrum, the gastric tissue makes contact with the hydrogel (**a**) and migrates along its surface (**b** & **c**) until it reaches the most distal portion of the gel where it causes retropulsion (**d**).

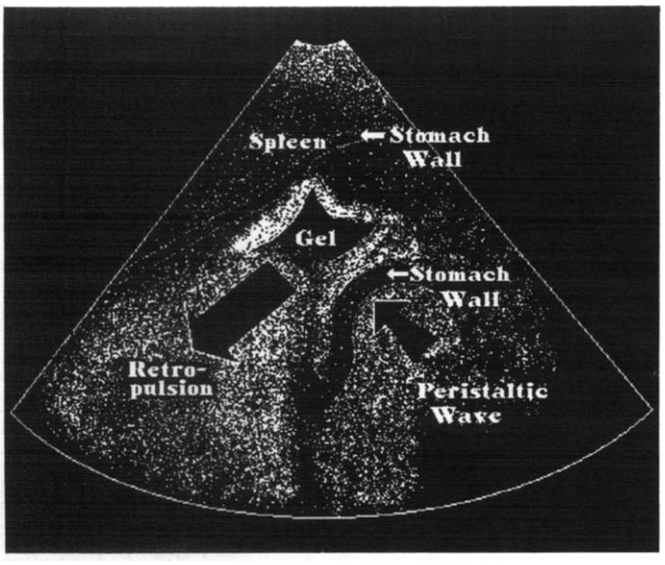


**Figure 4** Graphic illustration of the retropulsion phenomenon as seen through ultrasound imaging. Repetitive retropulsion in the pyloric antrum occurred when the peristaltic contractions of the gastric tissue engaged the hydrogel.

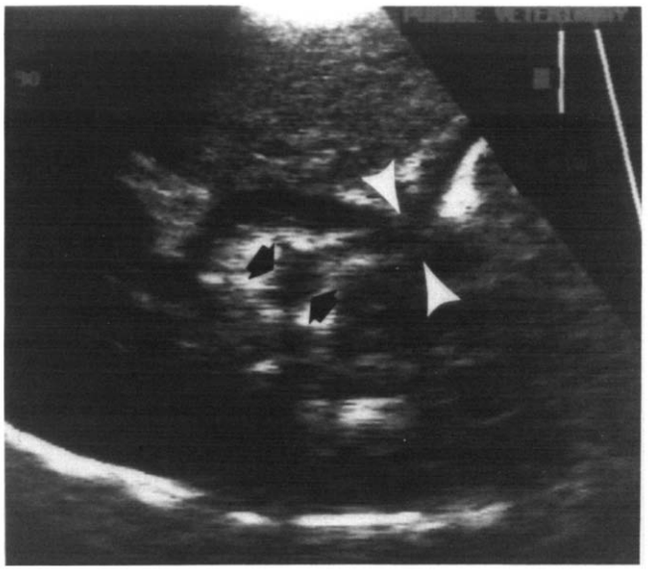

**Figure 5** Sagittal ultrasound image of the stomach with the hydrogel (between black arrows) aligned with the pyloric sphincter (between white arrow heads). This phenomenon preceded gastric emptying and occurred when the stomach was empty of fluid.

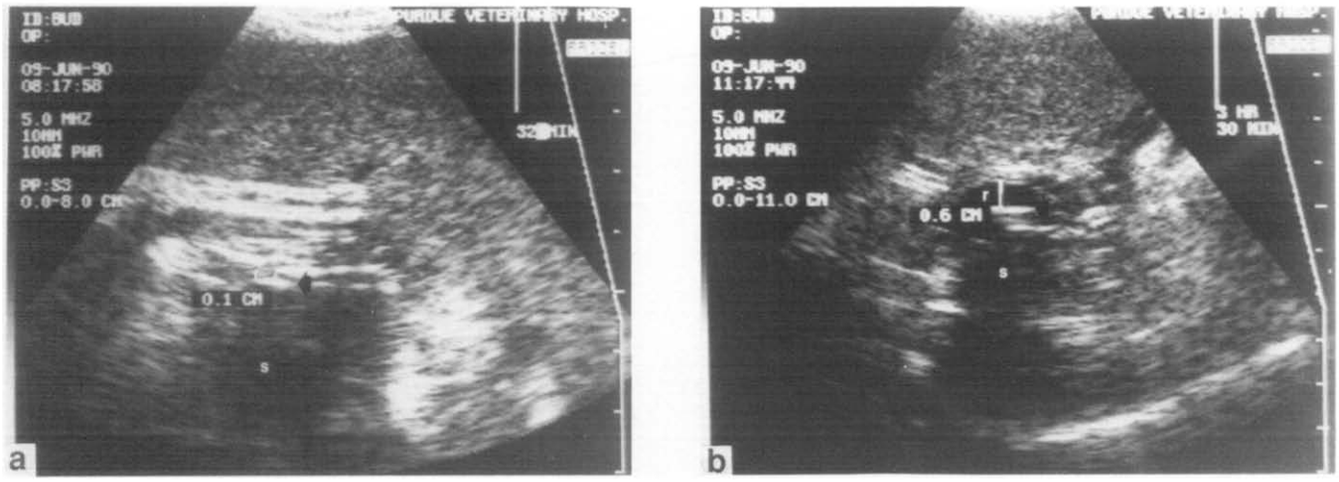


**Figure 6** Sagittal ultrasound image of the stomach depicting a partially swollen hydrogel. The rubbery outer layer of the gel is sonolucent and marked 'r'. The glassy/rubbery interface is represented by the bright echo marked by the black arrow. Since sound wave transmission was impaired due to the glassy core, an acoustic shadow marked 's' was present in the far field. Solvent penetration into the gel increased the thickness of the rubbery layer from 0.1 cm after 0.5 h in the stomach (**a**) to 0.6 cm after 3.5 h in the stomach (**b**).

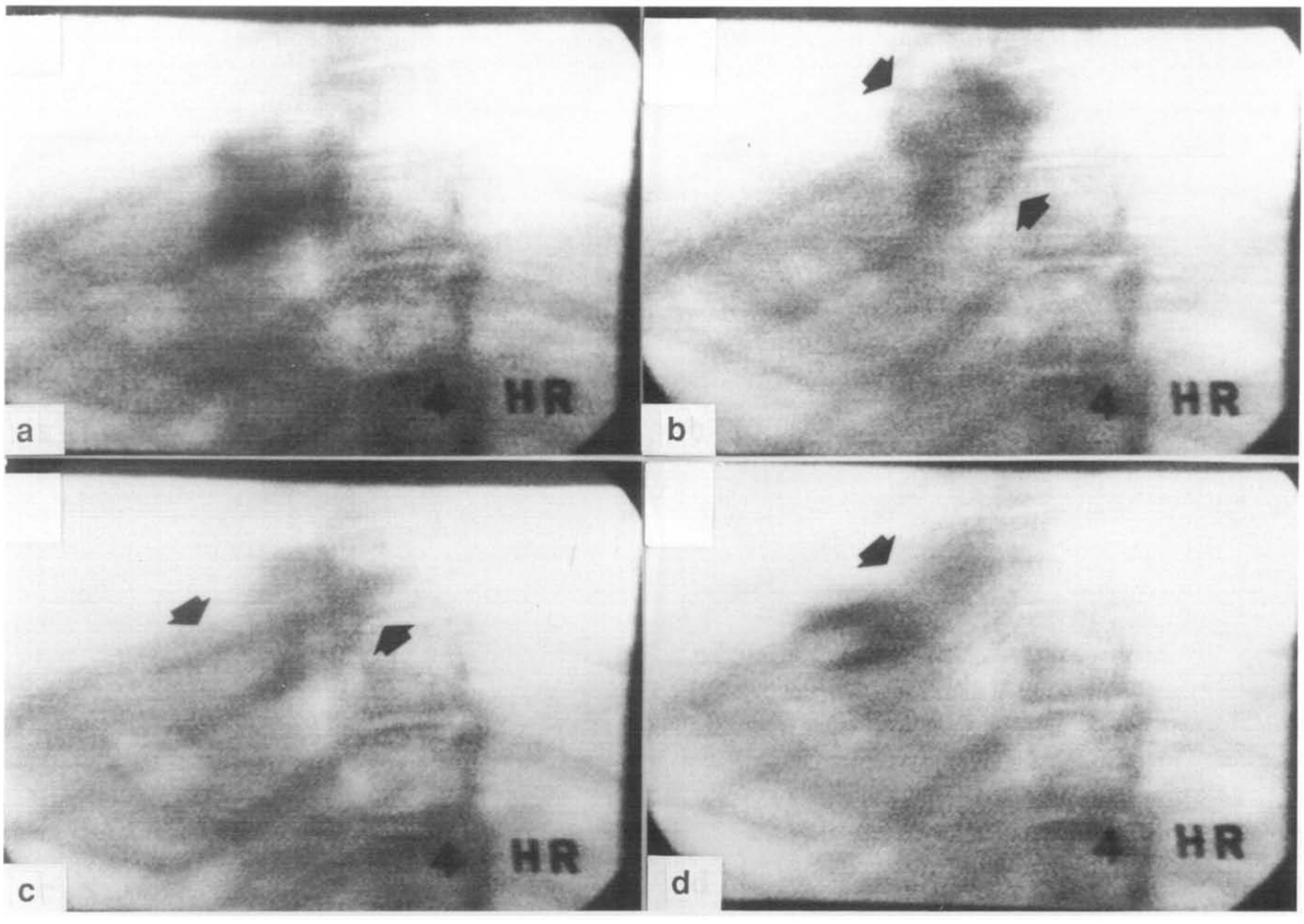


**Figure 7** Fluoroscopic images of the fully swollen hydrogel in response to a migrating peristaltic contraction (arrows). As a peristaltic contraction moved through the pyloric antrum (**a**), the hydrogel became deformed (between arrows in **b**) as it was compacted against the pyloric sphincter (**b**). When the peristaltic contraction moved over the gel (**c**), deformation was enhanced as the gel became elongated (arrows in **c**). The hydrogel (arrow in **d**) was subsequently retropelled once the peristaltic contraction reached the distal end of the gel (**d**). The fully swollen gel was retained in the stomach for 5 h.

(*Figure 6a*) in the stomach to 0.6 cm after 3.5 h (*Figure 6b*) in the stomach.

## Fluoroscopic imaging

In the absence of water in the stomach, ultrasound imaging of the hydrogel became difficult due to the presence of gaseous particles in the stomach lumen. Therefore, fluoroscopic imaging was also used to help monitor the dynamic movements of the gel in the fasted stomach. A typical response of a fully swollen hydrogel (2.3 cm in diameter by 1.6 cm in length) to peristalsis is shown in *Figure 7*. *Figure 7a* shows the hydrogel residing in the pyloric antrum. As the peristaltic contraction moved from left to right through the pyloric antrum, the hydrogel (between arrows in *Figure 7b*) became compacted against the pyloric sphincter. In *Figure 7*, the pyloric sphincter is located in the upper right-hand corner of the fluoroscopic images. Further migration of the contraction over the gel produced significant deformation of the hydrogel (arrows in *Figure 7c*). The hydrogel was subsequently retropelled toward the body of the stomach once the contraction reached the distal end of the hydrogel (arrow in *Figure 7d*). Within 5 h after administration, however, the fully swollen hydrogel had emptied from the stomach as an intact bolus. In the second set of experiments, the dynamic responses of the partially swollen hydrogel (2.7 cm diameter; 2.7 cm length) were examined. A typical response of the partially swollen hydrogel to peristalsis is shown in *Figure 8*. *Figure 8a* shows the hydrogel residing in the pyloric antrum. As the peristaltic contraction moved from left to right through the pyloric antrum, the gel was pushed against the pyloric sphincter (*Figure 8b*). It should be noted, however, that the extent of the gel deformation was far less than that of the fully swollen hydrogel observed in *Figure 7b*. Further migration of the contraction along the surface of the gel resulted in only slight deformation of the gel (arrows in *Figure 8c*). *Figure 8d* shows the retropulsion of the hydrogel toward the body of the stomach once the migrating gastric contraction reached the distal end of the gel. Unlike the fully swollen hydrogel, deformation of the partially swollen gel was limited to the outer rubbery edges. Under fasted conditions, the partially swollen hydrogel was retained in the stomach for 24 h. Over the 24 h fasted period, the dynamic movements of the gel in response to the gastric contractions remained the same as those shown in *Figure 8*.

## DISCUSSION

The main advantage of using real-time ultrasound imaging was that the dynamic events of the stomach, the gastric tissue–gel interactions, and the penetration of solvent into the hydrogel could be monitored simultaneously without the aid of radiopaque materials or radiolabels. The main disadvantage in ultrasound imaging

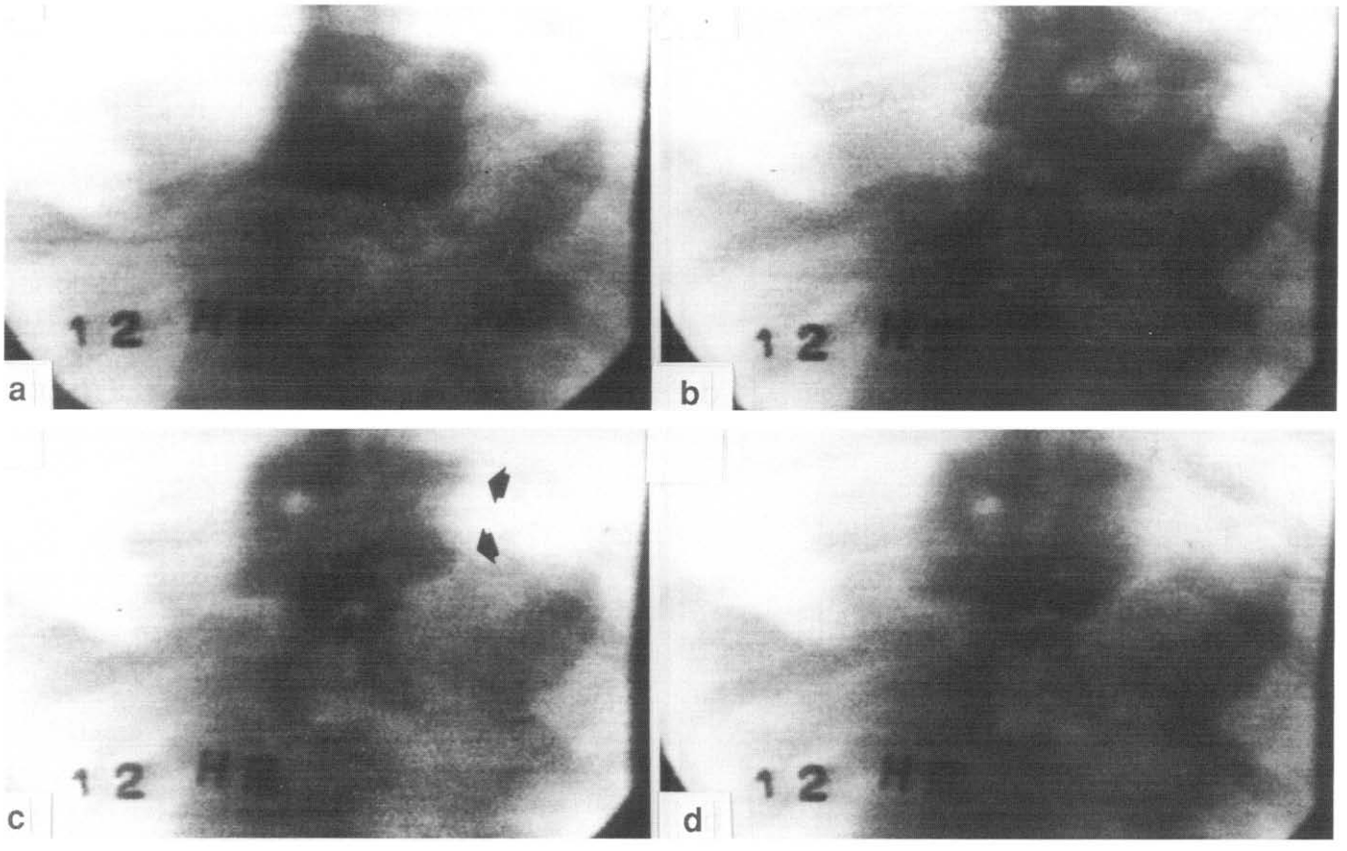


**Figure 8** Fluoroscopic images of the partially swollen hydrogel in response to a migrating peristaltic contraction. As a peristaltic contraction moved through the pyloric antrum (**a**), the hydrogel was pushed against the pyloric sphincter with no apparent deformation (**b**). When the peristaltic contraction moved over the gel (**c**), the deformation was limited to the edges of the gel (arrows in **c**). Retropulsion occurred with minimal deformation of the gel (**d**). The partially swollen gel was retained in the fasted stomach for 24 h.

was the difficulty in imaging the hydrogel once most of the water had emptied from the stomach. Ultrasound imaging detected the hydrogel, the gastric tissue, and the water in the stomach based on the acoustic impedance mismatch at the respective interfaces[29, 30]. When the hydrogel was partially swollen, the glassy/rubbery swelling front provided a significant acoustic impedance mismatch to produce a bright echo at the interface (*Figure 6*). An acoustic shadow also developed in the far field of the image since the sound waves could not penetrate the glassy core of the gel and were subsequently reflected at the glassy/rubbery interface. With the rubbery or fully swollen hydrogel, the transmission of sound waves through the gel was not impaired since the acoustic impedance of the fully swollen gel was similar to that of the aqueous surroundings. As a result, the hydrogel was detected as a sonolucent object once the glassy core had disappeared after swelling (*Figures 1–5*). Ultrasound imaging could also detect the gastric tissue and the hydrogel concurrently by the same principles mentioned above. Thus, it was very effective in studying the changes in the gastric tissue–gel interactions and the movements of the hydrogel in response to these interactions. When the lumen was largely distended with water, the degree of gastric tissue–gel interactions was low and as a result, the peristaltic contractions were ineffective in driving the gel toward the distal region of the stomach. As the lumen of the stomach became less distended, the ability of the peristaltic contractions to drive the gel toward the pyloric antrum was enhanced due to the increase in the gastric tissue–gel interactions during peristalsis. In this study, the degree of gastric distention was only qualitatively estimated since a sagittal view of the stomach was imaged. It should be pointed out that the degree of gastric distention has been quantitatively determined with a transverse view of the stomach lumen[31–33]. In man, ultrasound imaging has its limitations. If images of the body/fundus region of the stomach are to be obtained, ultrasound imaging may be time consuming due to anatomical variations and body weight differences[34]. When images of only the pyloric antrum are required, however, ultrasound imaging has been shown to be very effective and less time consuming[31].

In the absence of water in the stomach, a significant acoustic impedance mismatch occurred at air/gastric tissue interfaces to impair the transmission of sound waves through the lumen of the stomach. For this reason, it became increasingly more difficult, but not impossible, to image the hydrogel with ultrasound in the absence of water. In this case, fluoroscopic imaging was a good alternative in visualizing the dynamic movements of the hydrogel in the stomach. Through fluoroscopy, differences in the hydrogel deformation during peristalsis were readily detected as a function of the solvent content inside the gel. By using both ultrasound and fluoroscopic imaging, we could make direct and indirect assessments of the glassy core of the hydrogel. Our study suggests that the glassy core of a partially swollen hydrogel might have a dramatic effect on prolonging the gastric retention time of the gel. The presence of the glassy core reduced the deformation of the hydrogel in response to peristalsis and apparently impaired the ability of the peristaltic contractions to push the gel through the pyloric sphincter. If only radiographic images were made of the hydrogel, the dynamic events related to gastric retention could not be appreciated. Since the glassy core is thought to be the reason for the gastric retention of hydrogels in the fasted state, the effects of gel integrity on gastric retention warrants further investigation. The advantage of using fluoroscopic imaging over ultrasound imaging was that the gel could be located and monitored more readily under fasted conditions. The main disadvantage of using fluoroscopic imaging is that the dynamic movements of the gastric tissue cannot be directly visualized and the differences in the physical properties of the hydrogel are only indirectly assessed with the aid of contrast medium.

The performance of a controlled release device for oral drug delivery is dependent on its GI residence time, its drug releasing properties, and the physicochemical properties of the drug. When the intended drug possesses a short half-life and restricted absorption in the upper GI tract, maintaining prolonged therapeutic levels of the drug in the blood by the oral route can only be accomplished through a multiple dosing regimen or by a device that can reside in the upper GI tract. When multiple dosing results in drug toxicity problems or reduced patient compliance, however, utilizing the latter approach may be therapeutically more effective. Physiologically, the most suitable site for the retention of dosage forms in the upper GI tract is in the stomach[35]. Thus, it is important to understand how oral dosage forms can be manipulated to overcome premature gastric emptying. Through ultrasound and fluoroscopic imaging, the response of oral dosage forms to dynamic events in the stomach may be studied more effectively, and the factors that contribute to gastric retention can be examined.

In both human and animal studies, $\gamma$-scintigraphy has been the technique of choice in the study of the GI transit of both digestible and non-digestible materials. $\gamma$-Scintigraphy is non-invasive and exposes the subject to only low doses of radiation. A disadvantage of this technique for the study of gastric retention is that only the labelled material can be monitored over time. When the stomach contains a radiolabelled, yet swellable controlled release device, $\gamma$-scintigraphy will provide little or no information regarding the degree of solvent penetration into the device, the integrity of the device over time, and its interactions with the gastric tissue. Consequently, it may be more efficient to combine ultrasound and fluoroscopic imaging with $\gamma$-scintigraphy to study the gastric retention of controlled release devices in the GI tract. Ultrasound and fluoroscopy could examine specific properties of the device whereas $\gamma$-scintigraphy would monitor the GI transit of the device. Even though the combination of fluoroscopy and ultrasound with $\gamma$-scintigraphy may not be as useful in man due to excessive exposure to radiation, anatomical variations, and body weight differences, its use in animals may be quite promising.

In summary, ultrasound and fluoroscopic imaging can be utilized to obtain information relevant to the development of long-term oral drug delivery systems. The two imaging techniques can be used independently or simultaneously to visualize oral dosage forms and their interactions with the gastric tissue. These techniques

should find wide applications in the study of gastric retention of various materials.

## ACKNOWLEDGEMENTS

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