JPP Journal of Pharmacy and Pharmacology

JPP 2002, 54: 1351–1356

Received April 10, 2002
Accepted June 14, 2002
ISSN 0022-3573

# Echo-planar magnetic resonance imaging of Gaviscon alginate rafts in-vivo

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**Abstract**

Liquid Gaviscon and Gaviscon Advance are established reflux suppressant formulations. This study describes the use of echo-planar magnetic resonance imaging (EPI) to visualise non-invasively intragastric alginate rafts of Liquid Gaviscon and Gaviscon Advance in healthy subjects. Secondly, the feasibility of using relaxation rate ($T_2^{-1}$) measurements to monitor changes in the physicochemical properties of the rafts in-vivo is evaluated. Six subjects ingested 500 mL of a liquid meal and received a single dose of 20 mL Liquid Gaviscon or 10 mL Gaviscon Advance on 2 separate visits each and were imaged every 15 min. An alginate raft was observed in the stomach for all subjects and both treatments. The raft was observed to consist of a few large fragments on the majority of the scans for both products. At t = 60 min a raft was still present in all cases. Three-dimensional volume reconstructions showed, for the first time, the spatial distribution of the rafts within the gastric lumen. The $T_2^{-1}$ data showed potential for assessment of dynamic changes in the physicochemical properties of the alginate rafts in-vivo. We conclude that EPI shows great potential in assessing alginate rafts formation in-vivo.

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**Acknowledgement and funding:** We gratefully acknowledge Dr Ron Coxon, Dr Andy Peters and Mr Paul Clark for technical assistance. This work was funded by Reckitt Benckiser Healthcare (UK) Limited, Hull, UK.

## Introduction

Liquid Gaviscon and Gaviscon Advance are established formulations acting as reflux suppressants by forming an alginate raft that floats on top of the stomach contents, thus providing a physical barrier to reflux into the lower oesophagus. The formation of alginate raft is key to the mode of action of such products (Mandel et al 2000) in the treatment of gastro-oesophageal reflux disease (GORD) and the ability to study the raft in-vivo would facilitate investigation of the effect of formulation modification on their performance.

The formation and retention of alginate rafts in-vivo has been investigated previously with radiolabelled medication using gamma scintigraphy methods (Washington & Denton 1992). This technique has proved to be successful although it yields poor spatial resolution and exposes subjects to ionising radiation.

Over the last decade, several reports have proved the potential of magnetic resonance imaging (MRI) (Schwizer et al 1992) and in particular of its snapshot variant echo-planar imaging (EPI) (Stehling et al 1989; Evans et al 1993) in monitoring gastric function. MRI collects signal from the water hydrogen protons in the sample following a radio-frequency excitation. Such signal is spatially encoded using magnetic field gradients and subsequently an image can be reconstructed. The EPI technique can acquire a whole image (usually with 128 by 128 pixels resolution) in under 130 ms. This speed can effectively freeze physiological body motion, hence EPI is particularly suited to image moving organs like the stomach, providing detailed images of the gastric lumen and its contents and of dynamic processes taking place within it (Wright et al 1996).

An abstract reporting a preliminary positive experience of visualisation of Gaviscon rafts using MRI was recently published (Paterson et al 2000). Such data substantiate the

hypothesis that MRI could provide a unique tool to carry out in-vivo monitoring of alginate rafts. Furthermore, the true snapshot nature and the inherent contrast that EPI provides between gel materials and liquid meals could be advantageous in visualising the alginate rafts in the gastric lumen, without the need for doping the alginates with MRI contrast agents which might alter the physicochemical properties of the alginate (Paterson et al 2000). EPI can also monitor non-invasively the intragastric viscosity of polysaccharide gels in-vivo by exploiting the relationship between one of the standard measurable parameters, the transverse relaxation rate ($T_2^{-1}$), and gel viscosity (Marciani et al 1998, 2000). Hence, EPI might provide useful information on the physicochemical properties of alginate rafts in-vivo.

Therefore, the aims of this pilot study were firstly to evaluate the potential use of EPI to visualise alginate rafts in-vivo following ingestion of a liquid test meal and a single dose of Liquid Gaviscon or Gaviscon Advance in healthy subjects. Secondly, to evaluate the feasibility of using $T_2^{-1}$ measurements to indicate changes in the physicochemical properties of the rafts in-vivo.

## Materials and Methods

The main study was preceded by in-vitro and in-vivo optimisation phases to determine the appropriate EPI scanning sequences and parameters to be used.

Six healthy subjects (4 male, 2 female, mean age 22±3 years) of normal height and weight (mean body mass index 23±2), with no history of gastrointestinal disorders and taking no regular medication, attended on 2 separate morning sessions each, having fasted overnight.

The study was an open, randomised, single-centre study, designed as follows (Figure 1): at each morning session a preliminary volume scan was performed to verify that the subject's stomach was empty. Subjects were then asked to ingest 200 mL of 150 kcal fat pre-load (Fortisip, Nutricia, Zoetermeer, Holland) to switch from fasting to fed motility throughout the experiment. Twenty minutes later they were asked to ingest, within 10 min, 500 mL of a liquid test meal (60% water, 10% table sugar and 30% lemon juice). Immediately after ingestion, a baseline volume scan was acquired and this was defined as experimental time t = 0. Five minutes later, subjects received a single oral dose of 20 mL Liquid Gaviscon or 10 mL Gaviscon Advance (Reckitt Benckiser Healthcare (UK) Limited, Hull, UK) according to an open randomisation list to avoid order effects. They were then positioned supine on the scanner bed outside the magnet bore, and remained in this position between consecutive scans. Fifteen minutes later, one volume and one $T_2^{-1}$ data set were acquired. This was repeated every 15 min until the stomach appeared to be empty. Five minutes after that, subjects were asked to drink rapidly 500 mL water to refill the stomach and a final volume scan was acquired to detect any retained raft fragments.

All subjects gave informed written consent before experiments. This study was approved by the University Medical School Ethics Committee and was conducted according to ICH-GCP standards.

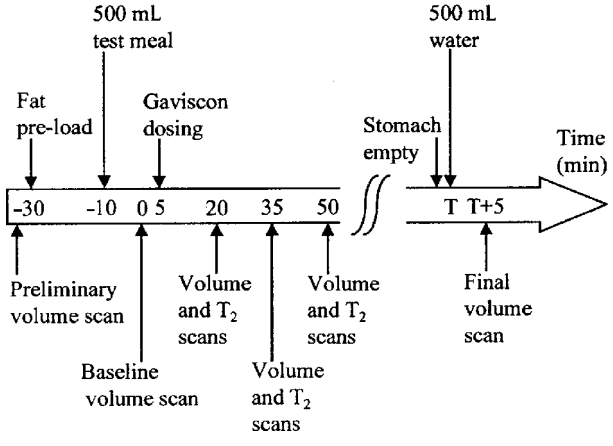


**Figure 1** Schematic description of the experimental design.

### Magnetic resonance imaging

Single-shot half Fourier EPI (Howseman et al 1988) images were acquired on a whole-body 0.5 T purpose-built EPI scanner equipped with actively shielded gradients and a 50-cm diameter bird-cage coil. The in-plane resolution was 3.5 mm × 2.5 mm and a slice thickness of 1 cm was used throughout the experiments. Each image was acquired in less than 100 ms using a 128 × 128 matrix with an echo time of 20 ms. Transverse, multi-slice, volume sets of images were acquired from oesophagus to duodenum (total acquisition time 4 s). After the volume set, a $T_2$ data set was acquired on the gastric contents using a multiecho EPI sequence (Tyler et al 2000) with four echo times varying from 74 to 731 ms, repeated 3 times, with a repetition time of 10 s (total acquisition time 45 s). Subjects were instructed to hold their breath before each image acquisition, to minimise diaphragmatic displacement.

### Data analysis

Images were analysed by one operator using Analyze software (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN). Volumes were calculated by drawing a region of interest around either the raft or the meal on each image of the multi-slice volume sets and summing the areas across the slices. The transverse relaxation rate ($T_2^{-1}$) was measured for both the raft and the meal at each time point. $T_2^{-1}$ data were processed as described previously (Gowland et al 1998). Results were expressed as mean ± s.e.m. Neither sample size power nor specific statistical analysis calculations were planned in the study protocol, as this was a feasibility study. Paired *t*-test, Wilcoxon's signed rank test, analysis of variance or Page's non-parametric trend test for ordered treatments were used as appropriate. Study procedures and data recording were monitored and all data underwent quality assurance audit.

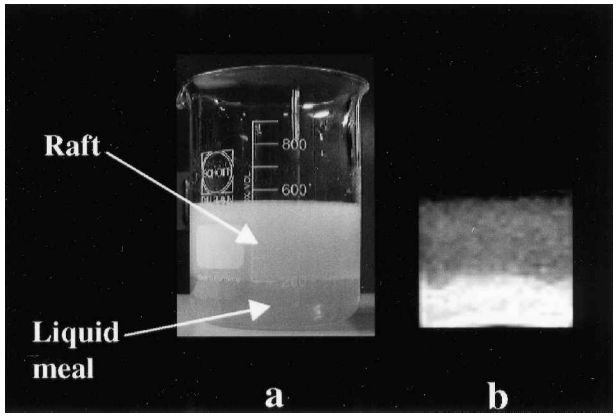


**Figure 2** Digital photograph of a beaker containing a Liquid Gaviscon raft floating above a lemon juice and water solution (A) and correspondent EPI image (B). In the EPI image the raft appears darker than the liquid meal due to the inherent $T_2$ contrast of the EPI imaging module and to the gelly nature of the raft, which restricts water protons mobility. The susceptibility effect of the $CO_2$ gas within the raft also contributes to the contrast mechanism.

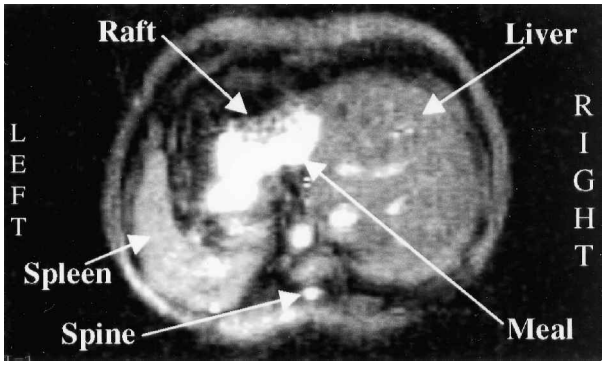


**Figure 3** Example EPI image of a Liquid Gaviscon raft in-vivo. The subject was lying supine in the scanner bore. Some anatomical landmarks are indicated to ease the reader's image interpretation. The raft is clearly seen floating at the top of the gastric lumen.

## Results

The alginate rafts were clearly visible in the EPI images with good contrast between the floating raft and the underlying liquid meal both in-vitro and in-vivo, as shown in Figures 2 and 3, respectively. The study procedures were very well tolerated by subjects.

It was possible to observe an alginate raft in the stomach for all 6 subjects and for both treatments from the initial (15 min) assessment. The raft was present in the stomach up until 90–135 min post-dose (median 112 min) for Gaviscon Advance and up until 75–120 min post-dose (median 105 min) for Liquid Gaviscon. After the stomach was refilled with water (post-meal emptying), an alginate raft was observed for all but two cases (that both involved Liquid Gaviscon), with one scan not performed due to a technical failure.

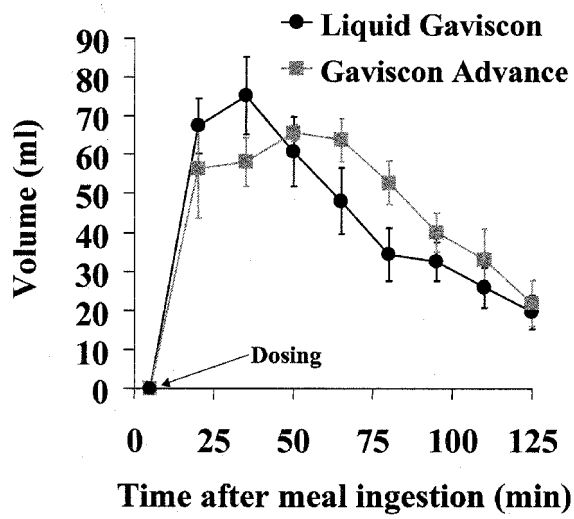


**Figure 4** Total volume of the alginate rafts (floating plus eventual sunk fragments) present in the gastric lumen calculated from the echo-planar magnetic resonance imaging volume scans and plotted versus time for both Liquid Gaviscon and Gaviscon Advance. Data are mean±s.e.m. from 6 subjects.

The alginate raft was observed to consist of a few large fragments on the majority of the scans for both products. In some cases, however, the raft was coherent (seen as a single unit with no intervening spaces), particularly for Liquid Gaviscon at 75 and 90 min post-dose. The raft was generally observed to be split (i.e. some fragments were floating and others sunk). The entire raft was sunk on some occasions, particularly at the first (15 min) scan for Gaviscon Advance. The entire raft was floating at later times (particularly at 75 and 90 min post-dose) for Liquid Gaviscon.

Meal volumes decreased over the study period, with no significant differences between the Gaviscon Advance and Liquid Gaviscon test sessions. Fifty-percent retention of the meal (as % of initial volume) was at 42 min (median) for Gaviscon Advance and 49 min for Liquid Gaviscon (signed rank test applied to within-subject differences, $P = 0.844$).

The total volume of the raft (floating plus sunk fragments) was calculated at each time point and plotted versus time (Figure 4). Maximum mean raft volume was achieved slightly earlier for Liquid Gaviscon (30 min post-dose) than for Gaviscon Advance (45 min). Raft volume declined more rapidly for Liquid Gaviscon than for Gaviscon Advance, the difference in raft volumes achieving statistical significance at 75 min post-dose ($P < 0.020$), with raft volumes similar at 120 min post-dose. At t = 60 min, when the total stomach contents were approximately half-emptied, a raft was still present in all cases and was at least partially floating in the majority of cases for both treatments.

When the stomach appeared empty in the images, volunteers drank a further 500 mL of water and another final set

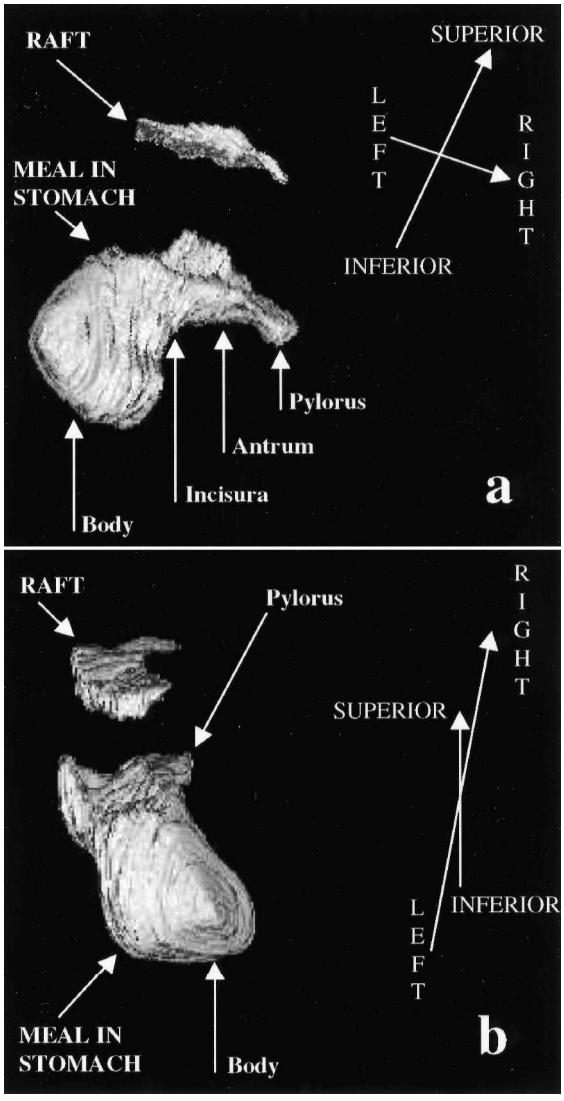


**Figure 5** The Gaviscon Advance raft and the underlying meal in the gastric lumen of a healthy subject (supine in the EPI scanner) reconstructed three-dimensionally from the volume set at t = 95 min. A and B. Two different views of the same reconstruction. The raft has been separated from the meal contents for clarity.

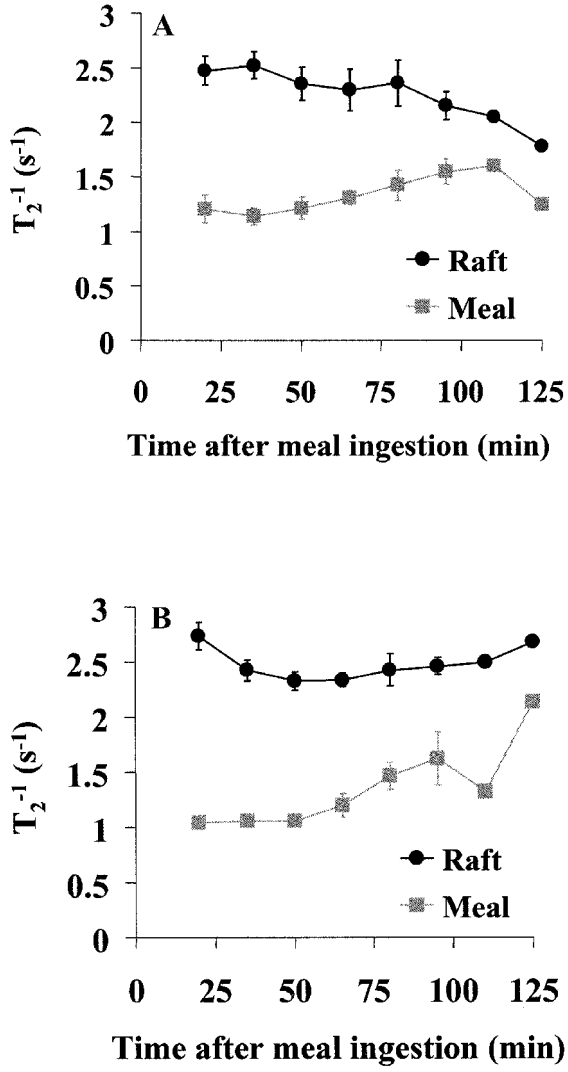


**Figure 6** Plots of the transverse relaxation rate ($T_2^{-1}$) of alginate raft and meal for Liquid Gaviscon (A) and Gaviscon Advance (B) with time after meal ingestion. Measurements were carried out in-vivo using a multiecho echo-planar magnetic resonance imaging sequence. Data are mean±s.e.m. from 6 subjects.

of images was acquired. A raft was observed to be still in the stomach in 60% of cases for Liquid Gaviscon and in 100% of cases for Gaviscon Advance.

Three-dimensional reconstructions of both the floating raft and the underlying meal were carried out from the volume sets for three subjects. An example is given in Figure 5 for Gaviscon Advance.

Plots of the changes in the transverse relaxation rate $T_2^{-1}$ measurements with time, for both the raft and meal, are shown in Figure 6A and 6B for Liquid Gaviscon and Gaviscon Advance, respectively. As expected, $T_2^{-1}$ values for the raft are higher than the $T_2^{-1}$ values of the liquid meal. Such difference is statistically significant at all time points up to 75 min with Gaviscon Advance and up to 90 min with Liquid Gaviscon, with very few data values recorded beyond these times.

$T_2^{-1}$ of the liquid meal shows a positive overall time effect (analysis of variance, $P < 0.001$), confirmed by statistically significant trend effects for each test products (Page's test, $P = 0.03$ for Gaviscon Advance and $P < 0.01$ for Liquid Gaviscon).

Overall, $T_2^{-1}$ of the alginate raft decreased with time ($P = 0.013$), but no evidence of a trend was found for either treatment when considered separately (Page's test, $P > 0.2$). The apparent divergence of raft $T_2^{-1}$ mean values at later time points shown in Figure 6B may be due to the small sample sizes involved. No statistically significant difference between treatments was found.

## Discussion

The results of this pilot study showed that EPI was able to visualise an alginate raft in-vivo in the stomach for all six subjects studied and for both Liquid Gaviscon and Gaviscon Advance. Good contrast between the raft and the liquid meal was found in the EPI images, such that the alginate raft looked darker than the bright liquid meal. This contrast reflected the different physicochemical environments of the raft and the liquid meal.

MRI images the hydrogen protons of water, hence the MRI signal is intimately linked to the physicochemical environment of the water protons in the sample, particularly proton exchange, and it has been used successfully to study gel materials. In this study, the rafts of both Liquid Gaviscon and Gaviscon Advance consist of an alginate gel matrix containing $CO_2$ gas micro-bubbles, and both these components will have reduced the relative signal from the raft compared with that from the liquid meal. Firstly, the alginate gel matrix restricts the rotational tumbling freedom of the water molecules trapped in it. Secondly, the water from the hydration layer around the gel can also exchange with gel hydroxyl groups and, if the exchange is fast on the nuclear magnetic resonance timescale, this can cause cross-relaxation and thus affect the raft MRI signal. Finally, the presence of the $CO_2$ gas micro-bubbles trapped within the raft disturbs the local magnetic field across the raft and this causes a further reduction in the acquired signal. In the liquid meal instead, the water molecules are free to tumble, hence the signal collected was higher than that from the raft.

In this EPI study it was possible to assess the presence, position and coherence of the alginate rafts. This was performed by simple visual analysis of each image volume set, utilising the good contrast between the raft and the meal in the images. Once the raft and the meal were visualised in a multi-slice volume measurement set across the gastric lumen, it was possible to perform, separately, raft and meal volume calculations for a given time point, using a commercial image analysis package. Meal volumes over the study period, as expected, decreased due to gastric emptying. The liquid test meal, crucial to gain contrast between the gastric lumen and the surrounding organs in the EPI images, remained in the stomach for up to approximately 2 h due to the fat/caloric pre-load given to the subjects before they ingested the test meal.

We used an acidified drink to accentuate the process of raft formation. We used a supine posture to perform the scans as our scanner could not be made vertical. This may not be ideal for assessing a floating product since its distribution depends on posture. However, recent technical developments have allowed manufacturers to produce upright, open design scanners that will, in the future, overcome this issue.

Raft volumes initially increased after dosage, particularly for Gaviscon Advance, presumably due to the continuing raft formation/aeration process. Maximum mean raft volume in-vivo was achieved slightly earlier for Liquid Gaviscon (30 min post-dose) than for Gaviscon Advance (45 min post-dose). This apparent slower raft formation dynamic for Gaviscon Advance agreed with preliminary in-vitro observations carried out with the same test meal for this study. Maximum mean raft volumes in-vivo were consistent with the volume of raft that 20 mL Liquid Gaviscon and 10 mL Gaviscon Advance would generate in-vitro. The total volumes of the raft (floating plus eventual sunk fragments) in-vivo subsequently declined more rapidly for Liquid Gaviscon than for Gaviscon Advance. After the stomach emptied the liquid component of the test meal, it became difficult to detect accurately any retained alginate raft due to the lack of sharp contrast between raft and liquid. Hence the subjects drank 500 mL of still water to refill the gastric lumen and facilitate detection of any retained raft. An alginate raft was retained in the stomach in 100% of cases for Gaviscon Advance and in 60% of cases for Liquid Gaviscon (with one scan not performed for Liquid Gaviscon due to a technical failure).

Three-dimensional reconstructions of both the raft and the underlying meal were obtained from the multi-slice volume sets. Such reconstructions, which can be viewed from any angle, showed for the first time the distribution of the raft above the liquid meal in the gastric lumen with high spatial resolution.

The transverse relaxation rate ($T_2^{-1}$) is one of the fundamental MRI parameters, which is well characterised theoretically and widely used experimentally. It simply reflects the time constant with which the system under investigation transfers energy to the surrounding environment. In this study, the difference in $T_2^{-1}$ between raft and liquid meal was expected because high water mobility is reflected in a low $T_2^{-1}$. Lower water mobility, fast proton exchange with the gel hydroxyls and $CO_2$ gas micro-bubbles all contribute to the higher $T_2^{-1}$ observed in the raft.

The interpretation of the observed dynamic changes in $T_2^{-1}$ values with time is, therefore, complex. The decrease in $T_2^{-1}$ values for the raft with time could be due either to a slow degrading of raft gel coherence (i.e. an increase in hydration and water mobility) or to a slow release of $CO_2$ gas micro-bubbles from the matrix (i.e. a reduction of the effect of the presence of the gas). However, the increase in the $T_2^{-1}$ of the liquid phase of the meal would suggest a slow leakage of degraded gel matrix into the meal with time. However, although the $T_2^{-1}$ data suggested that some physicochemical changes occurred in both the raft and the liquid meal with time (and perhaps between products), it was not possible to differentiate between the gel and the $CO_2$ gas effects from these data. Further work is needed to link $T_2^{-1}$ values to raft composition and, possibly, to raft rheology. The addition of different MRI measurements (such as proton density weighted MRI) to the $T_2^{-1}$ analysis of the rafts could assist in separating the effects of alginate and $CO_2$ gas.

### Conclusion

The feasibility of the use of EPI to visualise Liquid Gaviscon and Gaviscon Advance alginate rafts in-vivo, and hence to measure their retention and location within the gastric lumen, was demonstrated. The EPI investigation is safe and the study procedures were very well tolerated by

subjects and could easily allow serial studies and comparisons of different alginate raft formulations without the need to use radioactive labels or contrast agents.

The $T_2^{-1}$ data showed potential for assessment of dynamic changes in the physicochemical properties of the alginate rafts in-vivo. However, further investigation in-vitro is required to correlate meaningfully the $T_2^{-1}$ values to the dynamics of raft formation in-vivo.

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