Original Article

The rheological properties of an alginate satiety formulation in a physiologically relevant human model gut system

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Background: Satiety in the stomach is often caused by distension and the satiating feeling is triggered through afferent vagal signals. Increasing or prolonging the distension of the stomach with a low-calorie agent would be beneficial in reducing the energy intake and potentially aid in the management of weight. The aim of this work was to quantify the rheological properties of an alginate formulation to induce satiety (AFIS) as it passes through a physiologically relevant model of human digestive tract.

Methods: A physiologically relevant model of oral, gastric and small intestinal digestion was used to simulate *in vivo* conditions, including digestive capacity and physical forces. Samples were taken from the model and the rheological properties and viscosity of them assessed. This was repeated in the presence of a mixed meal.

Results: The addition of the AFIS gelled strongly in the gastric phase of the model gut system and reformed the gel after shear stress disrupted the gel network. The inclusion of the formulation to induce satiety with a mixed meal to the model gut system increased the viscosity in the gastric phase to a greater extent than just the formulation alone.

Conclusions: The forces generated by the stomach *in vivo* would be sufficient to eventually overcome the gelled formulation and with the repeated breakdown and additional gastric secretions would eventually allow passage into the small intestine. The synergistic increase in viscosity seen with the mixed meal and the formulation indicated an interaction between the formulation and the meal. The AFIS would potentially increase the retention time of gastric contents as well as gelling strongly. However, the forces generated by the stomach *in vivo* would eventually be sufficient to breakdown the formulation, and with the additional gastric secretion, allow it to pass into the small intestine, avoiding indefinite retention.

Keywords: Alginate; model gut system; satiety; gel; rheology

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Introduction

Satiety is a sensation of fullness which can result in a reduced drive to eat. This is brought about by various mechanisms following consumption of a meal with gastric satiation being volumetric and intestinal satiation being nutritive (1). In the stomach when it is distended the satiating feeling is triggered through afferent vagal signals (2,3) with stimulus from intraganglionic laminar endings (IGLEs), intramuscular arrays (IMAs) and mucosal afferents (4). The food structure and viscosity of the gastric contents also play a role modulating the time a meal is retained in the stomach.

The manipulation of these mechanisms is a potential method to reduce energy intake and aid weight management. The inducement of satiety may be preferable mode of weight management as many other forms of weight management often increase the feelings of hunger such as reduced portion size, reduction in calories diets, or increasing physical activity. Inducing satiety is an effective way to reduce appetite and reduce energy intake with a meal (2,5) however it is of great importance to the effectiveness of the product for a sustained feeling of satiety to ensure that the deficit in food/energy intake is maintained without next meal compensation (2).

Dietary fibres are by definition not digested in the upper digestive tract but the removal of dietary fibres from foods or meals has shown to decrease the time it takes for feelings of hunger to return (6) and increase the rate of gastric emptying (7-9). Many soluble fibres have the ability to increase viscosity (10) and some can gel at low pH inducing feelings of satiety (11), helping control appetite (12). The addition of these components to foods or through supplements has been a targeted mechanism to induce satiety by diet food producers over many years (2,13,14).

The consumption of high viscosity products is often unappetising so the ability to significantly increase viscosity or form gels after consumption is important for consumer acceptance and enjoyment (10,12,15). The speed and strength of the gelation would be important to maximise the mechanism of satiety triggered. Rapid gelation in the stomach could potentially increase the steric hindrance for digestive enzymes to break down chyme in the stomach, maintaining food structure and reducing gastric emptying (11). Also forming a strong and robust gel would distend the stomach triggering gastric stretch receptors (3,11,16-18).

One fibre that has been investigated to this end is alginate, a dietary fibre often included into food products as a thickener, emulsifier or stabiliser (E401-405) (19) but has been shown to have a more functional role in the gastrointestinal (GI) tract (20). Alginates can form both acid and ionic gels but have been shown to also reduce digestive enzyme activity (21-24) and potentially reduce circulating cholesterol, triacylglycerol and glucose (22,25-27).

The increase in viscosity or gel formation after the consumption of a product with alginate increases the likelihood of an appealing and acceptable product for consumers (15).

Alginates have been shown to reduce postprandial energy intake (28-31) but the optimisation of a formulation containing alginate to not only consistently gel rapidly and robustly regardless of buffering capacity of a mixed meal but also entrap and retain gas generated by the formulation to increase the volume of the gel would have potential to aid in appetite suppression, and weight management.

The aim of this study was to quantify the viscosity of a proprietary alginate formulation and its relevant rheological and viscoelastic parameters under physiological conditions as it passes through a model of the human GI tract. Quantifying the gelation and breakdown achieved and whether sufficient to stimulate satiety through gastric distension and be broken down and emptied from the stomach under normal gastric forces so as not to cause issues with retention. These parameters have been collected in the presence and absence of a mixed meal.

We present the following article in accordance with the MDAR reporting checklist (available at https://aoe.amegroups.com/article/view/10.21037/aoe-20-89/rc).

Methods

Materials

The proprietary alginate formulation, alginate formulation to induce satiety (AFIS) (composition in *Table 1*) was a gift from Technostics (Hull, UK) and was stored at room temperature until required.

The mixed meal was a 'Double Sausage and Egg McMuffin' with a regular (300 mL) black coffee (McDonalds, Newcastle, UK), 34 g fat, 28 g carbohydrate, 2.5 g fibre, 2.7 g salt, and 36 g protein, as previously used as standard meal in alginate studies (32).

All reagents for the model gut systems were purchased from Sigma (Poole, Dorset, UK) with the exception of the enzymes pepsin (Affimetrix, High Wycombe, UK), gastric like lipase (Amano Enzyme Inc., Nishiki, Japan) and bile (of porcine origin) which was collected fresh from 30 animals at a local abattoir, pooled and frozen in aliquots until required.

Table 1 The composition of the proprietary alginate formulation

Component	Amount (g) per 12.81 g dose
Sodium alginate Manugel GMB	1.50
Calcium carbonate	0.70
Sodium bicarbonate	0.50
Glucono-delta-lactone	2.80
Malic acid	0.05
Isomaltose	7.00
Sucralose	0.02
Vanilla flavour	0.24
Total	12.81

The composition of the model gut solutions are described in detail by Houghton *et al.* [2014] (33).

As this is an *in vitro* study, there were no patients or human tissue involved in this study and thus the requirement of ethical approval and informed consent were waived.

Study methods

Model gut system

The methodology of Houghton *et al.* [2014] (33) was followed with some minor adjustments, described as follows. AFIS was added to 100 mL of vortexing (300 rpm) deionised water and allowed to mix for 1 minute before the synthetic saliva was added and in turn added to resting gastric juices. The gastric phase of the model was performed in a bag mixer (400S, Interscience, Saint-Nom-la-Bretèche, France) generating the same forces as gastric contractions, as observed in the stomach *in vivo* by Koziolek [2015] *et al.* and Cassilly *et al.* [2008] (34,35).

The gastric secretions (5 mL) were added every 10 minutes over the 60 minutes of the gastric phase. At the end of the gastric phase the contents were added to pre incubated bile (37 ℃) and the pancreatic secretions continuously added over the two hours of the small intestinal phase of the digestion model as described by Houghton *et al.* [2014] (33). The same protocol was followed with and without AFIS present.

Mixed meal model gut system

The same model gut system procedure was followed as for the model gut system however a mixed meal of 'Double Sausage and Egg McMuffin' with a regular (300 mL) black coffee was homogenised (Cookworks handheld stick blender, Argos, Newcastle, UK) for 30 seconds before the AFIS was added. The same protocol was followed with and without AFIS present.

Pressure measurements during gastric phase of the model gut system

A digital pressure meter (MH3111 Sika Chipping Norton, UK) was attached to the paddle of the bag mixer and data logged using EBS 20 M software (Greisinger, Regenstauf, Germany). The measurements were made for the midpoint (30 minutes) and full (60 minutes) through the gastric phase of the model, to account for the volume change caused by the gastric secretions.

Viscoelastic properties

Samples of the digesta (3 mL) from the model gut system were taken at 0, 30, 60, 61, 120 and 180 minutes in the model. The linear viscoelastic region (LVER), breakdown point (the transition from gel to viscous liquid, $\delta>45°$) and subsequent breakdown points (transition from gel to viscous liquid after the gel has reformed after the force was removed) were measured at 37 ℃ using a Kinexus Pro Rheometer (Malvern Panalytical, Malvern, UK) using 40 mm serrated parallel plates with a 1 mm gap.

Viscosity

Samples of the digesta (1 mL) from the model gut system were taken at 0, 30, 60, 61, 120 and 180 minutes in the model. Increasing shear rates were applied (table of shear rates) and measured at 37 ℃ using a Kinexus Pro Rheometer (Malvern Panalytical, Malvern, UK) using a 60 mm 1° cone plate. The shear ranged from 0.1 to 100 s^{-1}. The pH of the gastric phase of the model gut system as adjusted to pH 6.5 to assess the effect on the sample viscosity. The viscosity (consistency) constant K was calculated using the power law equation.

Statistical analysis

The comparison of viscosity between the standard pH and the higher pH used in the gastric phase of the model gut system was performed by one-way ANOVA. The comparison between LVER, breakdown shear stress and viscosity of AFIS in the 'model gut system (MGS)' with and without food was also performed by a one-way ANOVA.

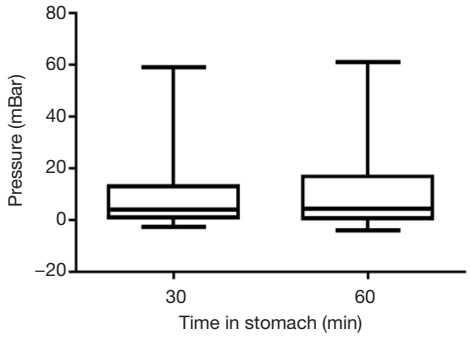

Figure 1 The minimum, maximum and mean pressures measured with volume of fluid equivalent to 30 and 60 minutes in the gastric phase of the model gut system.

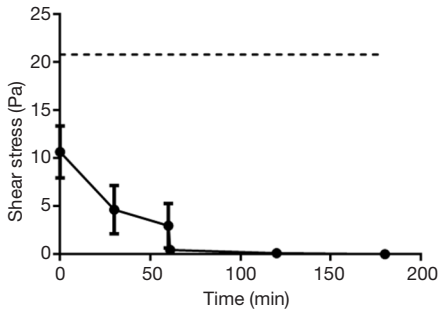

Figure 2 The linear viscoelastic region (LVER) of AFIS as it passes through the model gut system without food. The samples taken at various time points throughout the model gut system. The dashed black line indicates the breakdown shear of the AFIS before it has entered the model gut system. The baseline LVER value of model gut system without the AFIS at the corresponding timepoints has been subtracted as a background control. The experiments and background controls were repeated 3 times. AFIS, alginate formulation to induce satiety.

All values are shown as mean ± standard deviation, unless otherwise stated. All experiments were repeated 3 times.

Results

The mean pressure measured in the gastric phase of the model with the appropriate volume at 30 minutes was 10±13 and 11±15 mBar at 60 minutes. The maximum pressures were 59 and 62 mBar and the median were both 4 mBar for 30 and 60 minutes duration in the gastric phase (*Figure 1*).

Throughout the gastric phase of the model gut system, AFIS retains a LVER greater than 3±2 Pa, however once the conditions change to small intestinal like environment the LVER is greatly reduced (*Figure 2*). AFIS that has not been added to the model gut system has a LVER twice that of the initial measurement in the MGS, 10±3 *vs.* 21±18 Pa, but the model gut system had 50% additional volume.

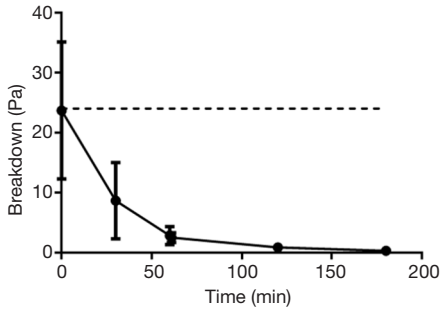

Figure 3 The shear stress required to break the gel in the model gut system without food. The samples taken at various time points throughout the model gut system. The dashed black line indicates the breakdown shear of the AFIS before it has entered the model gut system. The shear stress value for the model gut system alone, without the AFIS has been removed as a background control. The experiments and background controls were repeated 3 times. AFIS, alginate formulation to induce satiety.

The yield stress required to disrupt the AFIS gel is unaffected by the addition of saliva and resting gastric juice, 24±14 *vs.* 24±11 Pa without additional 50% volume (*Figure 3*). It is only with repeat breakdown of the gel structure through application and removal of force as well as the addition of gastric secretions that the breakdown point is lowered. This continues through the gastric and the small intestinal phases of the model. Although the samples remain a gel at all timepoints through the model but only at a shear stress below 3±2 Pa in the gastric phase and 0.4±0.3 Pa in the small intestinal phase.

As shown with the rheology of AFIS as is passes through the MSG, the viscosity is also reduced as it progresses (*Figure 4*). From the initial measurement in the gastric phase, a reduction of 9±7 (SEM) Pa·S over the hour of the gastric phase. Increasing the pH of the gastric phase did not significantly alter the initial or final viscosity of AFIS in the gastric phase and there was no statistical difference measured halfway through the gastric phase at 30 minutes.

When AFIS was tested with a mixed meal there was a larger initial LVER (accounting for the effect of food) at the start of the gastric phase than when the AFIS alone was digested through the MGS 34±31 (SEM) Pa *vs.* 116± 1 (SEM) Pa (*Figure 5*). In comparison with the food alone through the MGS the AFIS and food through the gastric phase has a greater LVER, although once into the small

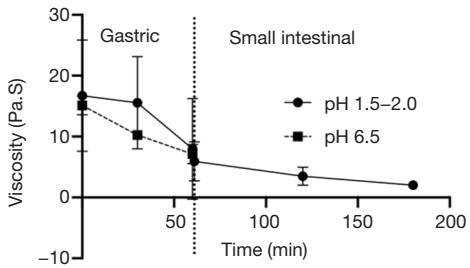

Figure 4 The viscosity of AFIS as is passes through the model gut system without food. The black line indicates the standard model gut system maintaining normal pH in the gastric phase. The dashed line indicates an increased pH in the gastric phase from its standard pH1.5 to pH6.5. The samples taken at various time points throughout the model gut system. The viscosity of model gut system alone at the corresponding timepoints has been removed as a background control. The experiments and background controls were repeated 3 times. The dashed vertical line indicates the transition from gastric to small intestinal phase of the model. AFIS, alginate formulation to induce satiety.

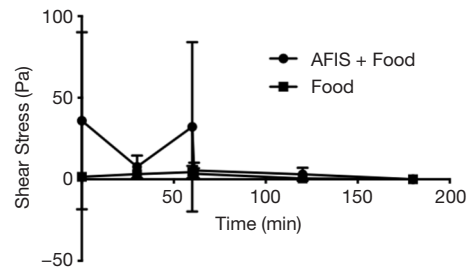

Figure 5 The linear viscoelastic region (LVER) of AFIS with food and food alone as it passes through the model gut system. The samples taken at various time points throughout the model gut system. The experiments and background controls were repeated 3 times. AFIS, alginate formulation to induce satiety.

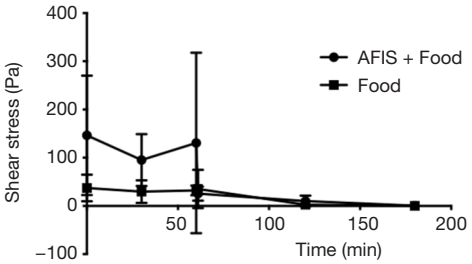

Figure 6 The shear stress required to break the gel in the model gut system of AFIS and food as well as food alone. The samples taken at various time points throughout the model gut system. The experiments and background controls were repeated 3 times. AFIS, alginate formulation to induce satiety.

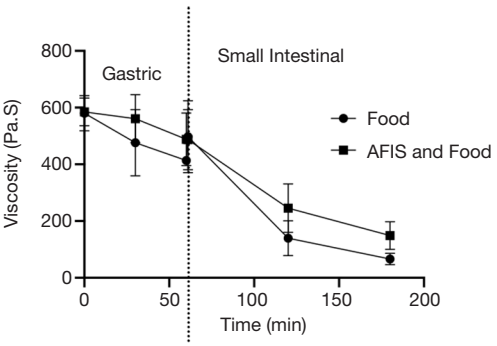

Figure 7 The viscosity of AFIS with food and food alone as is passes through the model gut system. The experiments and background controls were repeated 3 times. The circular symbols represent the viscosity of the mixed meal as is passes through the model gut system. The square symbols represent the viscosity of the combination of food and AFIS as it passes through the model gut system. The dashed horizontal line indicates the transition from gastric to small intestinal phase of the model gut system. AFIS, alginate formulation to induce satiety.

intestinal phase of the model there is little difference between presence and absence of food.

The shear stress required to disrupt the gel and make it flow is much greater in the gastric phase for AFIS with food than it is with the food alone (*Figure 6*). Although during the small intestinal phase of the model there is no statistical difference seen between AFIS and food combined (146± 124 Pa) compared to the food alone (37±28 Pa). It would be expected that due to the similarity between the food with and without AFIS in required breakdown force to make the gastric contents flow, the AFIS would pass through the small intestine as the meal would.

The viscosity of AFIS taken in combination with food also decreases through the MGS (*Figure 7*). The initial viscosity of AFIS with food and the food alone is very similar, however, the viscosity of the AFIS and food together remain higher than the food alone at 30, 60, 120 and 180 minutes.

Discussion

The forces generated by the stomacher mimic the forces observed in the stomach *in vivo* by Koziolek [2015] *et al.*

Figure 8 The effect of viscosity on time to half gastric emptying. Data taken from Marciani *et al.* [2000] and Ehrlein *et al.* [1987] to estimate the half gastric emptying time.

and Cassilly *et al.* [2008] (34,35). The forces, as described by Koziolek, are highly variable between volunteers but with very few measurements above 100 mbar. The maximum measured pressure in the 20 volunteers tested was 496 mbar but mean maximum of 293±109 mBar. Cassilly *et al.* (35) similarly describe the pressures generated within the stomach with both smart pill and fixed pressure catheter showing the majority of the first two hours in the stomach being greater than 10 mmHg (over 1,300 Pa, 13 mBar).

As the gastric phase of digestion is where volumetric satiety would be induced (1), the force required to breakdown the gel and cause it to flow would be a major factor in determining the satiety effect (3). The same shear strain was required to breakdown the AFIS gel alone as was required for the AFIS gel at the initial stages of the gastric phase which would have had oral and gastric secretions equivalent to an additional 50%. This highlights the ability of the AFIS to retain its gelled strength in the stomach and the potential satiating affect.

The additional volume of oral and gastric secretions does lower the LVER, the range of shear strain that does not affect gel properties, but more importantly the force required to break down the gel remained unchanged.

Repeated breakdown of the gel in the gastric phase does weaken the gel by reducing the force required to disrupt the gel but the gel does reform each time. Gastric emptying rates could be inferred from data taken for humans and dogs by Marciani *et al.* [2000] and Ehrlein *et al.* [1987] (36,37). *Figure 8* demonstrates the relationship between viscosity and time it takes to empty half the gastric contents. Both Marciani *et al.* [2000] and Ehrlein *et al.* [1987] measured the viscosity of a meal before it was consumed, and the half gastric emptying times in the stomach. Using the viscosity of AFIS at the initial phase of the model gut system a time to half gastric emptying can be estimated at 32 minutes. The addition of a mixed meal increased the viscosity 30-fold but is unlikely to increase the half gastric emptying time by a similar amount, as it is hypothesised that an increased meal viscosity would be partially compensated for with increased gastric secretions, however the retention time would still be greatly increased (38).

The repeated disruption of the gel and the addition of gastric secretions reduce the gel breakdown point as it moves through the model gut system. At the end of the gastric phase (60 min) the breakdown point is only 28% of what it was initially and when at the end of the small intestinal phase (effectively the ileum) the viscosity matches that measured by Ehrlein *et al.* in dog of 1.3–46 Pa·S (36).

Increasing pH of the gastric phase did reduce the viscosity of AFIS in the midpoint of the gastric phase but at the end of the model the viscosity was the same for both the higher pH gastric phase as well as the standard pH for the gastric phase (pH1.5). This indicates that although the acidity of the stomach may be beneficial for a high viscosity of the formulation it is the formulation itself that creates the optimum gelling condition for satiety, independent of physiologically relevant pH.

The inclusion of a mixed meal into the model gut system greatly increases the viscosity throughout the whole digestive tract model. At the mid-point and end of the gastric phase the AFIS increases the viscosity by more than just the viscosity of the AFIS alone. The increase in viscosity indicates an interaction between the AFIS and the food to generate the increased viscosity above that of the AFIS alone. Potentially the alginate in the formulation can interact with protein (39) but also the gelation of the formulation in the gastric phase of the model could prevent the breakdown of the food structure (40). Similarly, the LVER and the breakdown shear stress were also increased when combined with the mixed meal and were greater again with AFIS. Highlighting again, that AFIS can interact with components from the meal, increasing the force required to disrupt the gel.

The increase in rheological properties and viscosity with AFIS are more pronounced in the gastric phase of the model. The half retention time of the mixed meal with AFIS would be difficult to predict but would be significantly greater than that of mixed meal alone. However, the rheological properties and viscosity are comparable to that of the mixed meal alone during the small intestinal phase of the model.

These data suggest that the AFIS causes a strong gel in the gastric phase which would be retained in the stomach for longer than food alone and potentially when included with a mixed meal this may increase further. The forces of the stomach and the secretion of further gastric juice reduce the gel strength over time, which would allow the stomach to eventually empty the contents into the small intestines. This was estimated, and without a mixed meal the AFIS would take 32 minutes to be half emptied and the time greatly increased with a mixed meal.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. As this is an *in-vitro* study, there were no patients or human tissue involved in this study and thus the requirement of ethical approval and informed consent were waived.

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