

Modelling of physical and chemical processes in the small intestine

A. Tharakan^{1,2}, P. Rayment², P.J. Fryer¹ and I.T. Norton¹

1. Centre for Formulation Engineering, Chemical Engineering, University of Birmingham, Birmingham, B15 2TT, UK

2. Unilever Corporate Research, Unilever R&D Colworth, Sharnbrook, Bedford, MK44 1LQ, UK.

The chemical and physical processing of food in the small intestine is an important step for digestion. If foods are to be designed in the future to control digestion for impact on obesity and other dietary related chronic diseases, it is important to have realistic models of the processes that occur throughout the human gastrointestinal tract (GI tract). These models need to include how the food structure and viscosity affects enzyme reaction, how they impact on materials getting to the GI tract wall, how this affects the availability of the nutrients and how the flow patterns in the different parts of the GI tract impact on the food behaviour and breakdown.

In this paper we describe the design of an *in vitro* model of the small intestine section that allows investigation into the behaviour of the food and the delivery of nutrients to the intestinal wall while mimicking the physiological contractions of the small intestine.

By modelling the physical process conditions in the small intestine it has been possible to suggest effects that the soluble dietary fibre guar gum has on the delivery of nutrients to the intestinal wall. Soluble dietary fibres form viscous solutions that are non-Newtonian. Complex flows exist in the small intestine that affects the bulk viscosity experienced at different points in the contraction cycle. This may determine the rate of digestion of foods by changing delivery of nutrients to the intestinal wall and hence the rate and amount of absorption. The *in vitro* model has been used to measure the delivery of nutrients to the wall and shows a significant reduction in the rate of mass transfer across the membrane with a 1% weight by volume incorporation of guar gum under physiological flow conditions.

Key words: food design, in-vitro model, small intestine, guar gum

Introduction

Understanding the gastrointestinal tract

In order to exploit the opportunities of foods with health advantages due to their behaviour in the human digestive system, it is necessary to better understand and predict the digestion and subsequent metabolism of structured functional foods. Currently food product development uses mainly qualitative approaches to structure-function relationships that leads to cycles of prototyping and testing to develop the final product¹. As products become more sophisticated and require greater degrees of proof of function² the cost and time for development begin to escalate. The final steps and much over looked stage of food processing is the human digestive system (GI tract). The processing that the food undergoes in the human GI tract takes place in the mouth, stomach, small and large intestine (see figure 1). By (i) understanding the chemical and physical processes that the food goes through in the gastrointestinal tract and (ii) being able to model them appropriately, food product development time and cost may be reduced.

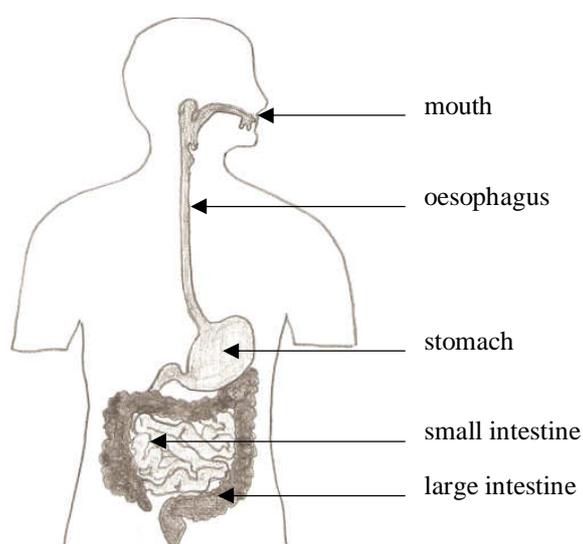


Figure 1: A diagram of the human digestive system

The small intestine was chosen as the area of focus initially as it is responsible for virtually all nutrient absorption and more than 95% of the water absorption in digestion³. Digestion and absorption in the intestine require not only constant mixing and ante-grade propulsion of the intestinal contents but also its local microcirculation across the absorbing surface of the epithelium⁴. The movements of the small intestine are responsible for the fluid dynamics and can be divided into *mixing contractions* and *propulsive contractions*⁵. The mixing contractions occur when a portion of the small intestine becomes filled with digesta (the food and intestinal secretions in the small intestine) and causes a localized concentric contraction and are spaced at intervals along the intestine⁵. The mixing contractions are known as segmentation contractions⁵. The propulsive contractions are responsible for propelling the digesta

through the small intestine and are known as peristalsis. They move analward at a velocity of 0.5 to 2.0 cm/sec, are normally very weak and die out after 3 to 5 centimetres⁵. Figure 2 gives a diagrammatic representation of these two movements. Better understanding of the small intestine will require similar studies to those conducted in the stomach using Magnetic resonance imaging (MRI)⁶⁻⁸; this will be possible in the near future.

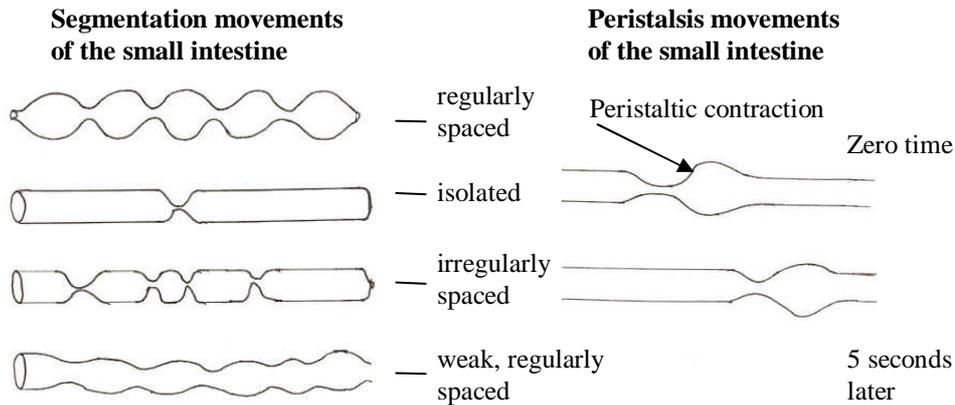


Figure 2: A schematic of the segmentation and peristalsis contractions found in the small intestine⁵

Molecules within the intestinal lumen are transported by diffusion or by convection set up by intestinal contractions which are responsible for the flow of the luminal contents. This flow is responsible for the mixing of substrate with enzymes but also the movement of nutrients close to the absorptive epithelium⁹. The nutrients then diffuse across a relatively unstirred layer to the epithelium where they are absorbed¹⁰. The *in-vitro* model is required to understand the mixing process in the small intestine.

Physical properties of food and nutrient delivery and health benefits

The physical form of food ingested and the physical properties of the intestinal contents produced can influence the rate of intestinal digestion, absorption and transit of the food. Certain soluble dietary fibres which form viscous solutions are known to reduce the rise in postprandial (after eating) glucose and insulin levels in man^{11;12}. Taylor and co-workers showed that guar gum has the greatest effect on glucose absorption compared with wheat bran, pectin, methylcellulose and gum tragacanth for the standard 50g glucose tolerance test. Results showed that for guar gum there was a reduction in the area under the one hour glycaemia curve of 68%¹³. Studies by Blackburn and co-workers showed that the presence of guar gum in glucose solutions fed to humans reduced the peak increase in blood glucose level by 50%¹⁰. This work concluded that guar improved glucose tolerance by reducing glucose absorption in the small intestine. They proposed that the mechanism of reduction is by inhibiting the effects of intestinal motility on fluid convection. There has been extensive study into the effect of guar gum on glucose absorption^{10;14-22}. Even with the large amount of information from clinical studies carried out assessing the efficacy of guar gum, the

understanding of the mechanism of action is still not defined²³ and this study attempts to address this. It is intended that the *in vitro* model will allow for further understanding of the physical and chemical processes taking place leading to the beneficial effect of guar gum by mimicking the process conditions seen in the small intestine.

Diabetes is a serious illness with several complications and premature mortality, accounting to at least 10% of total health care expenditure in many countries²⁴. There were estimated to be at least 170 million people with diabetes in the world in 2000²⁵. Being able to design foods that give more controlled glucose or other nutrient profiles would be of benefit to diabetics and those who are at risk of developing non insulin-dependent diabetes (NIDDM). The small intestinal model could aid in the development of such foods.

Chemical Engineering in the Small Intestine

The intestinal motility in the small intestine affects the fluid flow profiles of the digesta. The digesta is subject to widely different shear rates and other deformation modes such as extensional flow at different sites of the gut and at different times²⁶. The digesta is an extremely heterogeneous system to investigate and previous approaches have used simple guar solutions as model systems to provide some insight into effects of guar gum on reducing postprandial glycemia seen *in vivo*²³. By using pigs that were fed meals with and without guar gum Roberts and co-workers showed that the maximum zero shear viscosity of jejunal digesta ranged from 18 to 1454 mPa.s²⁷.

The transport phenomena in the small intestine are non-Newtonian fluid flow, convective mixing and diffusion of nutrients. There is also a reactive component between complex nutrients and the digestive enzymes that break them down into more simple nutrients that can be absorbed by the body.

The delivery of the nutrients to the intestinal wall, the convective mixing, diffusion and the kinetics of digestion could be influenced by the intestinal contents. To understand what is happening we need to apply engineering principles to quantify the processes within the system. This kind of understanding may enable the rational design of novel foods that breakdown and deliver macro and micro nutrients in the right place and at the optimal rate within the small intestine. Without such information the design of these foods will be purely empirical.

Digestion and absorption in the intestine require the mixing of the intestinal content and also the microcirculation across the absorbing surface of the epithelium⁴. To influence these processes it is important to understand and control the rheology of the fluid at the shear rates and flow profiles encountered in the GI tract. The shear rates and flow profiles have not been well established for the human small intestine although there is some information on other animal models albeit from taking visual parameters of small intestinal wall movements of a guinea pig and modelling the

expected flow profiles numerically²⁸. The fluid used and modelled for these studies was a saline solution which is a Newtonian fluid and therefore does not exhibit the shear dependant viscosity of the guar gum formulations. The numerical findings of Jeffrey and co-workers showed downstream and reverse flow, and vortical flow patterns that redistributed particles and mixed liquids²⁸. They also found that contractions generated pressures and shear stresses (maximum magnitude of 1.2 Pa) in particular along the moving section of the wall²⁸.

To be absorbed into the body, nutrient must pass through the epithelium which is a layer of cells that lines the wall of the small intestine and are connected by tight junctions. The cell wall of epithelium cells is made of a cell membrane with is a lipid bi-layer containing phospholipids, steroids and proteins²⁹. The mechanism of transfer through the membrane is described in Figure 3.

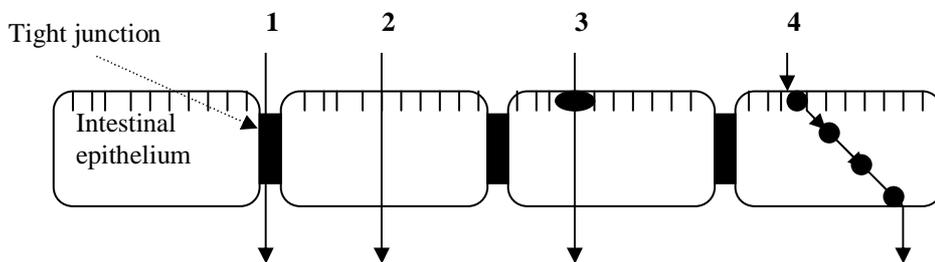


Figure 3: Mechanisms of transport across intestinal mucosa

1. Passage through the tight junctions between intestinal cells (paracellular transport). This is only for very small molecules and is driven by diffusion.
2. Passive diffusion of the compound through the cellular membrane.
3. Active transport using a specific transport protein present in the membrane that recognises the molecule for transport. Active transport requires some form of energy for this process (amino acids, iron and glucose are absorbed in this way).
4. Transcytosis is where the molecule is absorbed by pinocytosis and the vesicle is transported to the other side of the cell and then released.

However, to be absorbed the material must reach the membrane: here the complex mixing structures within the small intestine are critical. Flow in the small intestine is induced by the propulsive forces generated from the movement of the intestinal wall³⁰.

The characteristic Reynolds numbers of the overall flow are in the range 1×10^{-3} - 10 from fluid viscosities given by Roberts and co-workers²⁷ and the flow velocity given by Guyton⁵.

Our hypothesis is that the bulk processes are the rate-limiting step in the absorption process. There is evidence for this, as noted above, in that guar gum significantly decreases postprandial glycemia²³. However, this had never been tested as until now there has not been a realistic mechanical model to allow the parameters to be

controlled independently. We have developed a simple system with a non-active membrane to simulate the transport through the bulk fluid, to gain an estimate of the mixing processes in the small intestine.

A number of simulators for the gut have been proposed: Pal and co-workers developed a two-dimensional computer model of the stomach using the 'lattice-Boltzmann' numerical method from the laws of physics, and stomach geometry modelled from MRI³¹. This model was subsequently combined with *in vitro* experiments to quantify tablet erosion rate vs. surface shear stress³². Other mathematical models have been developed such as one of peristaltic flow and absorption in the small intestine by Leger³³ and one developed by Stoll and co-workers³⁴. Experimental models exist that are of various aspects of the gastrointestinal tract. A model of a segment of the small intestine was developed by Macagno and co-workers that investigated the effect of wall movement on absorption⁹. The Institute of Food Research (Norwich, UK) has developed a model of the stomach that simulates human digestion. TNO in the Netherlands have a model of the gastrointestinal tract that is a dynamic multi-compartmental system simulating conditions in the stomach and small intestine³⁵.

This paper describes the first mechanical model designed to simulate transport phenomena in the small intestine by mimicking the segmentation action. The work presents the design, development and the results from the experimental investigations using this novel approach. Investigations were carried out to understand how soluble dietary fibres influence the physical and chemical processes that affect the absorption of nutrients in the small intestine.

Materials and Methods

Materials

Model formulations of the fluid in the small intestine were made from solutions of guar gum and riboflavin in water. Guar gum is a biopolymer from a leguminous seed²³. Guar gum was the soluble dietary fibre of interest that forms viscous solutions. The guar gum used for these studies was purchased from Willy Benecke (Germany). Riboflavin (Vitamin B2) is essential for mammalian cells³⁶ and was used as the model nutrient for its fluorescent properties and low molecular weight of 376. The riboflavin was supplied from Sigma-Aldrich, Poole, UK. The membrane was a cellulose ester semi-permeable membrane (Spectra/Por 7, MWCO 8000 Daltons, size 8). The membrane was supplied from Medicell International Ltd, London, UK. A non-active membrane was chosen for the controlled investigation into the effect of the biopolymer on the rate of nutrient transfer across the membrane. The convection and diffusion through the bulk and near the wall of the membrane is simulating that of the small intestine up to the mucus layer and intestinal wall.

Methods

Formulation preparation

Initially a 0.1mM solution of riboflavin was prepared by dissolving the correct mass of riboflavin into water. To prepare the guar solution, a known weight by volume (w/v) of guar powder was slowly added to the riboflavin solution in a beaker being stirred using a magnetic stirrer. Once the guar had been added the container was weighed and the solution heated to 80°C and kept at 80°C for 10 minutes before cooling to room temperature, stirring throughout. Stirring continued for 12 hours to ensure complete hydration of the guar gum; the final concentration was calculated after finding the weight loss through evaporation. The containers used to store and prepare the riboflavin solutions were covered in foil to prevent light induced degradation of riboflavin. Concentrations between 0.1 and 1% were prepared by this method. The formulations were used within 24 hours of preparation as microbial growth after this time changes the properties of the formulation.

Material Characterisation

The riboflavin was characterised for fluorescence using a Perkin-Elmer Fluorimeter. The parameters for the fluorescence spectrophotometer were 488nm excitation and 522nm emission at 2.5nm slit widths. The rheological properties of the guar gum were characterised using a Physica UDS 200 rheometer (Anton Paar). Using the zero shear viscosities it was possible to determine the critical entanglement concentration for the polymer³⁷ (C^*) which was found to be 0.08% w/v.

Simple fluid mechanics

The diffusion coefficient of a nutrient through the fluid is an important parameter when considering the molecular delivery to the wall of the intestine. A common basis for estimating diffusion coefficients in liquids is the Stokes-Einstein (S-E) equation (1) which gives diffusion coefficients accurate to ~ 20%.

$$D = \frac{k_b T}{f} = \frac{k_B T}{6\pi\mu R_0} \quad (1)$$

Where f is the friction coefficient of the solute, k_b is the Boltzmann's constant, μ is the solvent viscosity, and R_0 is the solute radius and T is the temperature³⁸.

It is more common for engineers to think in terms of mass transfer. The advantage of this approach is that the mass transfer coefficient (K) relates the rate of mass transfer, mass transfer area, and the concentration driving force:

$$N_i = K\Delta C \quad (2)$$

Where N_i is the molar flux per unit area (mmol/m² s), K is the overall mass transfer coefficient (m/s) and ΔC is the concentration difference (mmol/m³).

The reciprocal of the overall mass transfer coefficient K can be represented by the sum of the guar side resistance, the membrane and the water side, represented by equation 3.

$$\frac{1}{K} = \frac{1}{k_{bp}} + \frac{l_{mem}}{D_{mem}} + \frac{1}{k_{rep}} \quad (3)$$

where k_{bp} is the biopolymer side mass transfer coefficient, D_{mem} is the diffusion coefficient of nutrient through the membrane, l_{mem} is the thickness of the membrane and k_{rep} is the recipient side mass transfer coefficient.

Results and Discussion

The small intestinal model

The small intestinal model (SIM) was designed to give a good representation of the flow and mixing in the small intestine. It consists of an inner porous flexible membrane and an outer flexible tube that is impermeable to water. As molecules diffuse through the inner tube membrane into the fluid contained in the outer tube they are detected by the fluorimeter using on-line sampling.

The segmentation action is responsible for promoting mixing of the solid food particles with the secretions of the small intestine⁵. In the model this action is reproduced by the inflation and deflation of a rubber cuff around the tube by alternatively applying compressed air and a vacuum. The mechanical squeezing mechanism was controlled by computer.

The small intestine is on average 6m in length and has a diameter ranging from 4cm at the stomach end to about 2.5cm at the junction with the large intestine²⁹. The diameter of the inner tube was 3cm and the length of the tube could be varied as required. The end result is a concentric mass exchanger that allows for the mechanical deformation of both the inner and outer tubes in a physiologically representative manner.

The mechanical squeezing mechanism was induced by the computer which controlled pneumatic inflation and deflation of the cuff wrapped around a section of the tube. The computer was used to control the inflation, deflation and delay times.

The layout of the SIM is shown in figure 4.

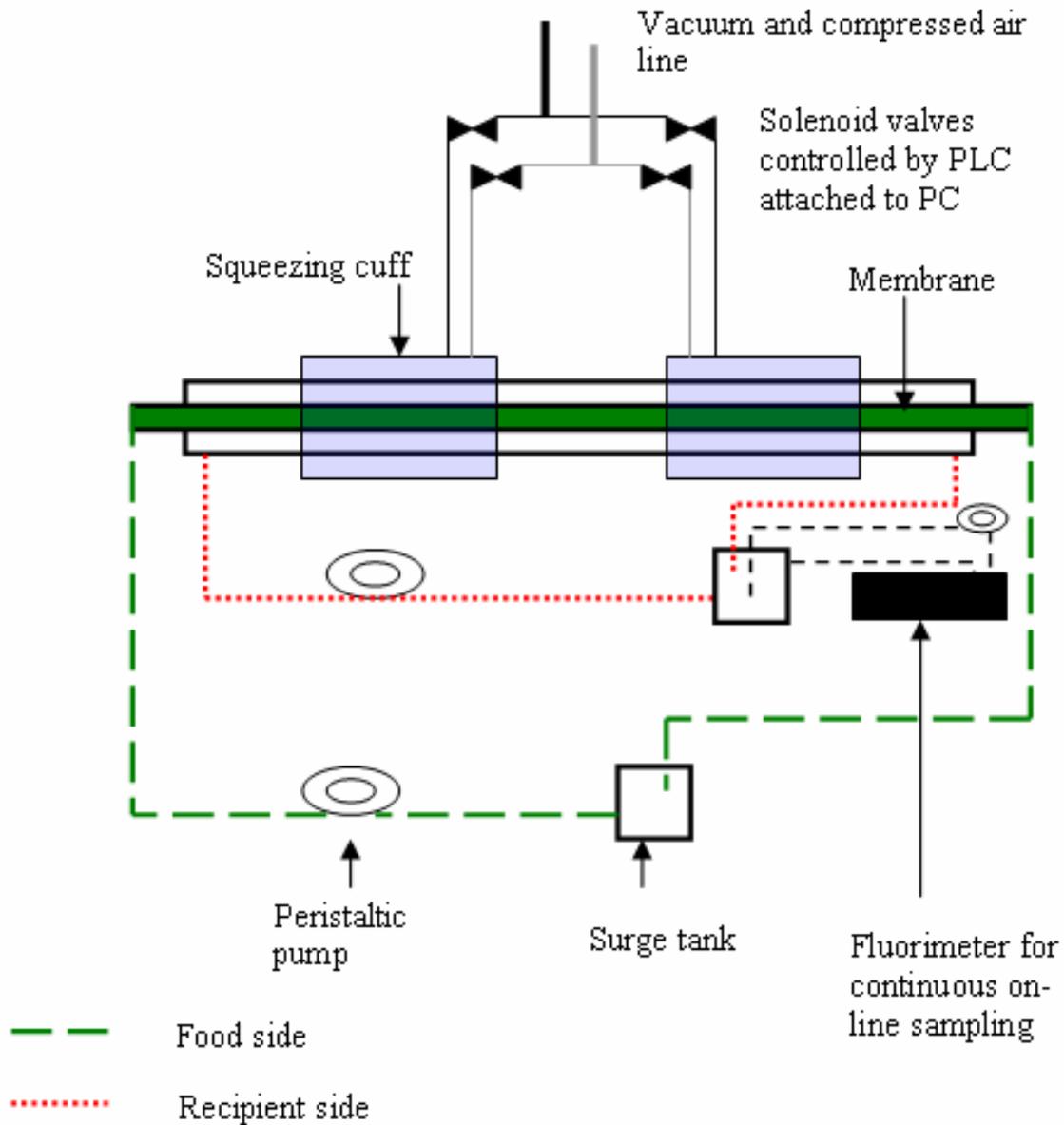


Figure 4: A schematic of the intestinal cell set up. Length of the mass transfer cell 0.5m, cuff length 0.12m, diameter of the inner tube 30.5mm, diameter of the outer tube 50mm. Food volume and recipient volume both 500ml.

Mass Transfer experiments using the SIM

A series of mass transfer experiments were carried out using the SIM. Formulations with differing guar gum concentrations were used for the experiments.

For each concentration of guar gum four processing conditions were investigated:

- no net flow induced by peristaltic pump *and* no squeezing by cuffs 1 and 2
- net flow induced by peristaltic pump *and* no squeezing by cuffs 1 and 2

- no net flow induced by peristaltic pump *and* local flow from squeezing by cuffs 1 and 2 alternatively with a 2 second inflation time, 2 second deflation time, 2 second delay and 0.5 barg inlet air pressure
- net flow induced by peristaltic pump *and* local flow from squeezing by cuffs 1 and 2 alternatively with a 2 second inflation time, 2 second deflation time, 2 second delay and 0.5 barg inlet air pressure.

These conditions were chosen to investigate the effect of (i) the flow induced by the peristaltic pump and (ii) squeezing to represent the segmentation action. Each experiment was carried out in triplicate and the mass transfer coefficient determined from the concentration time profiles, using equation 2.

Food side flow conditions were designed to represent as closely as possible to the net flow rate found in the small intestine⁵ of 1 cm/min. A peristaltic pump was used to give a volumetric flow of $1.2 \times 10^{-5} \text{ m}^3/\text{min}$ (a velocity of 1.6 cm/min) which was the minimum flow rate of the pump.

The Reynolds number was calculated using the zero shear viscosity. To obtain meaningful mass transfer coefficients it is important to calculate the Sherwood number, equation 4. The Sherwood number is a dimensionless number that is used in mass transfer studies to measure the mass transfer enhancement of systems with convection compared to diffusion alone.

$$Sh = \frac{k_{bp} L}{D} \quad (4)$$

Where k_{bp} is the biopolymer side mass transfer coefficient (m/s), L is the characteristic length (m) and D is the component diffusion coefficient (m^2/s). k_{bp} was determined from the experiments, L was taken as 0.0305m the diameter of the tube and D was taken as $4.97 \times 10^{-10} \text{ m}^2/\text{s}$ from the Stokes Einstein relationship as this gives an estimation of the diffusion coefficient in the system.

Table 1 shows the range of Reynolds numbers (0.00012-9) that are covered for the overall flow conditions of the experiment. The change is due to the variation in the zero shear viscosity from 8.9×10^{-4} to 7 Pa.s.

conc guar % w/v	Zero shear viscosity Pa.s	Flow velocity m/s	Diameter M	Density kg/m3	Re
0	0.00089	0.000274	0.0305	1000	9
0.1	0.004	0.000274	0.0305	1001	2
0.25	0.03	0.000274	0.0305	1002.5	0.3
0.5	0.35	0.000274	0.0305	1005	0.02
0.75	3	0.000274	0.0305	1007.5	0.0028
1	7	0.000274	0.0305	1010	0.0012

Table 1: Reynolds numbers of the system

Experiments to obtain the MTC were carried out for a range of guar gum concentrations (0, 0.1, 0.25, 0.5, 0.75, 1 % w/v) for the four processing conditions described above in triplicate.

In figure 5 typical data is shown of concentration versus time (water under squeezed conditions). A good linear regression (R^2 of 0.99) is obtained giving a gradient (2.66×10^{-6}) from which N_i is determined using the recipient side total volume (0.001 m^3) and the membrane surface area (0.05 m^2). This gives a flux of $5.32 \times 10^{-5} \text{ mmol/m}^2 \cdot \text{s}$.

By dividing the molar flux ($\text{mmol/m}^2 \cdot \text{s}$) by the concentration difference in mmol/m^3 gives the overall mass transfer coefficient K (from rearranging equation 2), as $5.32 \times 10^{-7} \text{ m/s}$.

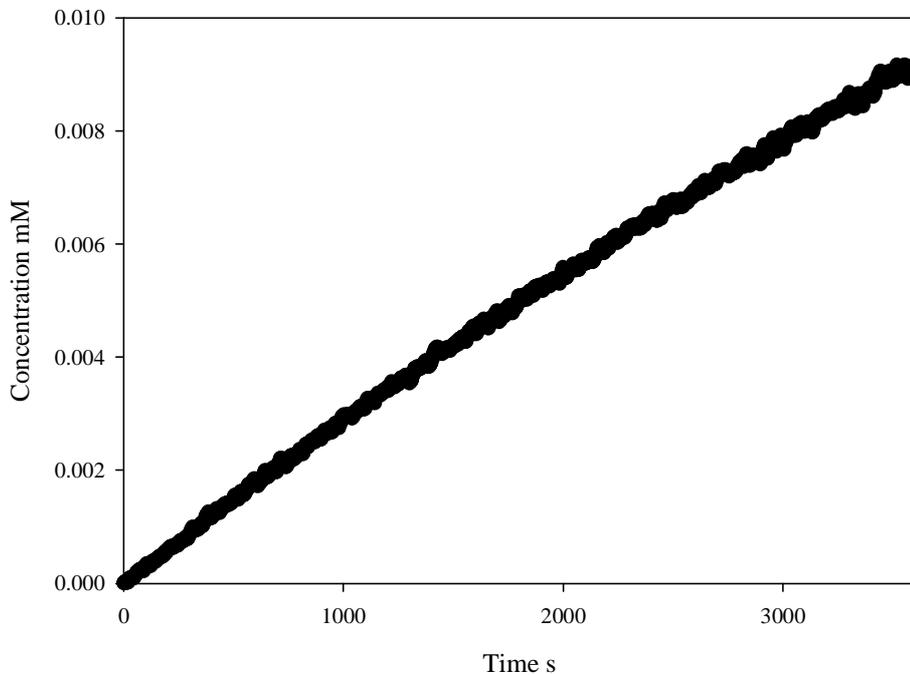


Figure 5: Example of trace that is obtained from experiment of concentration versus time

The overall mass transfer coefficient K , was found for the range of guar concentrations 0.1, 0.25, 0.5, 0.75 and 1% w/v under the four processing conditions: (i) no flow, no squeeze, (ii) flow, no squeeze, (iii) no flow, squeeze, (iv) flow, squeeze. The results for this are shown in figure 6.

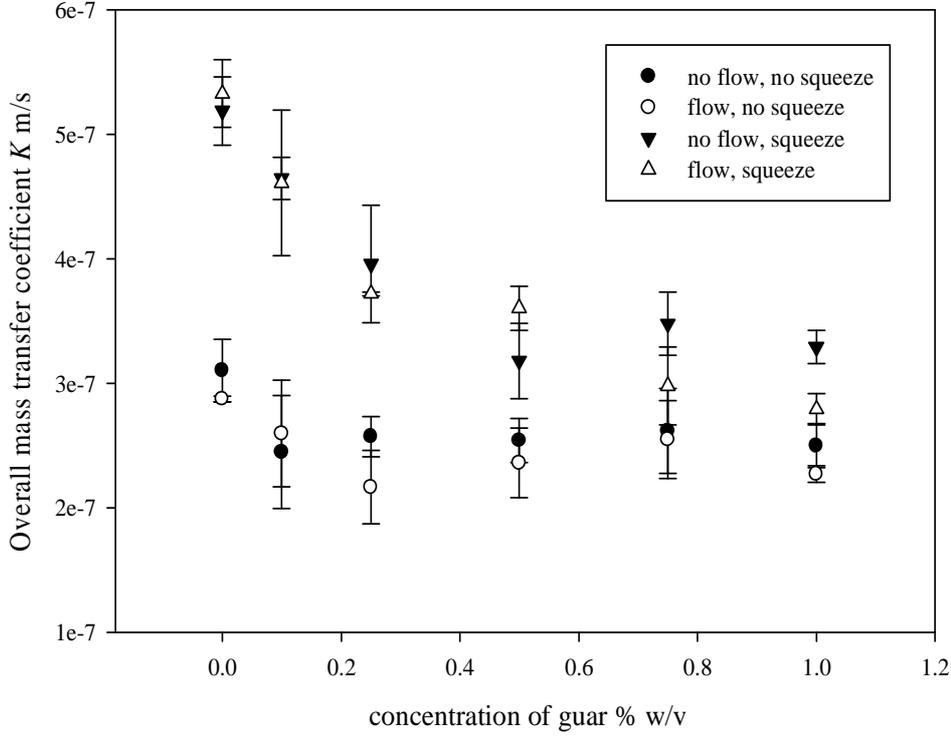


Figure 6: A plot of the overall mass transfer coefficient K versus concentration of guar for the four processing conditions: (i) no flow, no squeeze, (ii) flow, no squeeze, (iii) no flow, squeeze, (iv) flow, squeeze. The experiments were carried out in triplicate and the error bars show 1 standard deviation from the mean.

By using the maximum overall mass transfer coefficient K_{MAX} , found for water under the process conditions that minimise the tube side film resistance close to the membrane, it is possible to determine the system resistance (R_{system}), i.e. the combined resistances of the membrane (l_{mem} / D_{mem}) and the recipient side resistance ($1/k_{rep}$) assuming k_{bp} is then negligible.

$$\frac{1}{K} = \frac{1}{k_{bp}} + \underbrace{\frac{l_{mem}}{D_{mem}} + \frac{1}{k_{rep}}}_{R_{system}} \quad (3)$$

Where:

$$\frac{1}{K_{MAX}} = \frac{l_{mem}}{D_{mem}} + \frac{1}{k_{rep}} = R_{system} \quad (5)$$

k_{bp} the parameter of interest for the fluids containing guar is determined using:

$$k_{bp} = \frac{1}{\left(\frac{1}{K}\right) - R_{system}} \quad (6)$$

For experiments at different biopolymer concentrations and process conditions the overall mass transfer coefficients were found as on figure 6. By using equation 6 the biopolymer side mass transfer coefficient k_{bp} was then determined as on figure 7.

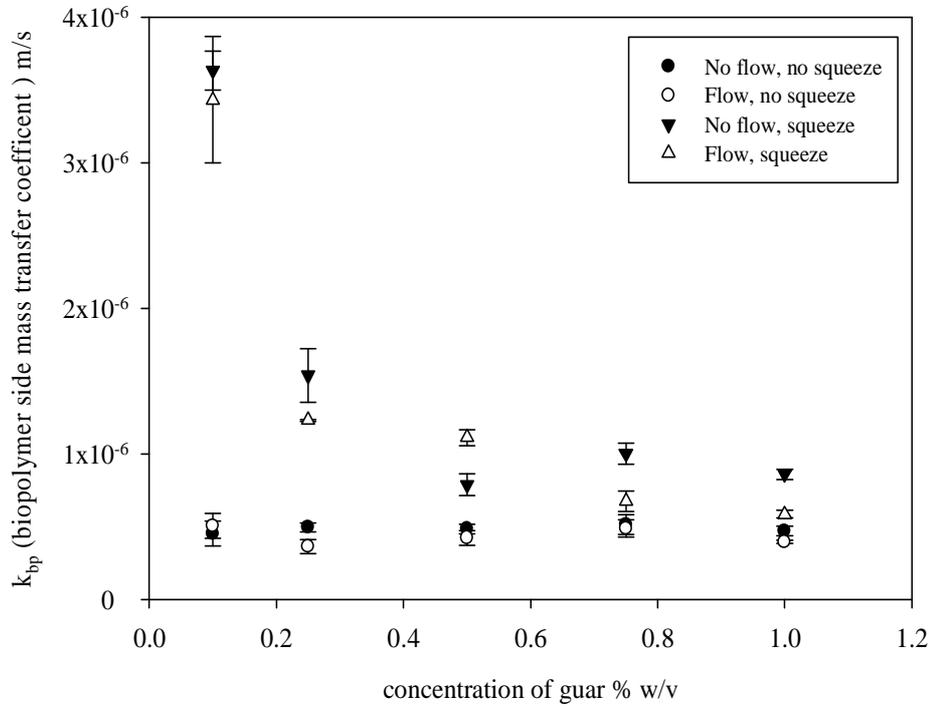


Figure 7: Plot of the guar side mass transfer coefficient at different guar concentrations in the intestinal cell under four processing conditions: (i) no flow, no squeeze, (ii) flow, no squeeze, (iii) no flow, squeeze, (iv) flow, squeeze. The experiments were carried out in triplicate and the error bars show 1 standard deviation from the mean.

Figure 7 shows (i) that the primary effects of mixing are due to squeezing; the tube side mass transfer coefficient k_{bp} is independent of the guar concentration, and therefore the viscosity of the system, without squeezing occurring. The k_{bp} without squeezing is also not affected by the flow induced by the peristaltic pump. (ii) when squeezing was carried out using 0.1% w/v guar the k_{bp} was increased from 5.0×10^{-7} to 34×10^{-7} m/s, by a factor of approximately 7. As the guar concentration is increased and therefore the viscosity is increased the effect of squeezing is reduced. At guar concentrations above $\sim 0.5\%$ there is no real difference between the squeezed and un-squeezed systems. It is hypothesised that the reason for the reduced mass transfer enhancement under squeezed conditions at guar concentrations above 0.5% w/v is that the resistance to flow (viscosity) prevents the enhancement from mixing.

The k_{bp} is made up of two components:

$$k_{bp} = \frac{D}{l} \quad (7)$$

Where D is the diffusion coefficient (m^2/s) and l is the film thickness (m). In the SIM it can be assumed that the diffusion coefficient is constant at a given guar concentration. Therefore any change in k_{bp} between squeezed and un-squeezed conditions is due to a change in the film thickness that is otherwise known as the boundary layer. At concentrations above 0.5% w/v there is negligible reduction in the film thickness due to the squeezing motion and this must be due to the increased viscosity.

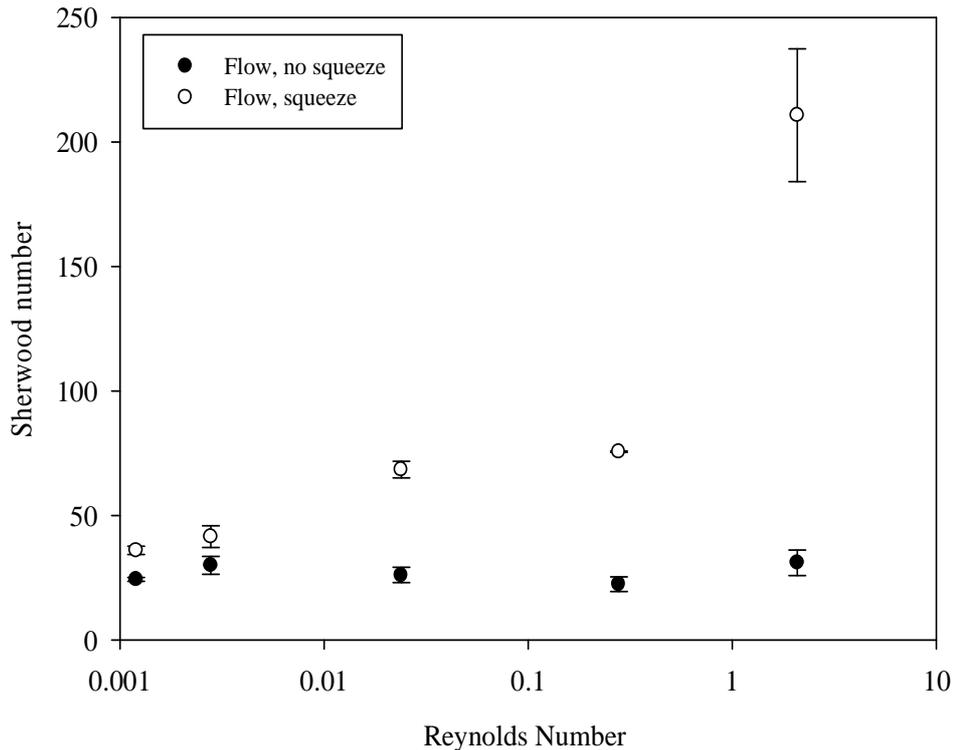


Figure 8: Plot of Sherwood number vs Reynolds number for experiments where there was squeezing by the two cuffs alternatively (2 second inflation, 2 second deflation and 2 second delay) and no squeezing. The Reynolds number was changed by manipulating the viscosity as the flow rate was kept constant.

Figure 8 shows that the Sherwood number is largely independent of the Reynolds number when there is flow in the cell but no squeezing, however, the Sherwood number increases as the Reynolds number increases for experiments when squeezing takes place. The increase in Sherwood number seen as the Reynolds number is increased is due to the mass transfer enhancement from mixing by reducing the viscosity of the fluid.

These results clearly show that the transport to the membrane can be controlled by the properties of the fluid under physiologically representative process conditions. The delivery of molecules to the membrane is largely unaffected by the peristaltic flow, but as the squeezing process will cause more mixing and flow close to the membrane surface there is an effect. As the concentration of the guar is increased under squeezed

conditions then the mixing and flow at the membrane surface is decreased resulting in the reduction of k_{bp} .

This type of model is simple but shows the sort of effects which may be seen in the body. Work is ongoing to make the experiment more realistic and study how digesta viscosity in the GI tract might affect nutritional delivery.

Conclusions

Experiments using the SIM have shown the significant effect that the segmentation motion has on the nutrient delivery to the intestinal wall as a consequence of changes in the mass transfer coefficient on the biopolymer side, k_{bp} . This is probably due to the increased mixing and a reduced boundary layer at the membrane surface. By increasing the bulk viscosity using guar there is no direct consequence on the mass transfer across the membrane if no squeezing action occurs. However, when the system is squeezed in a fashion resembling the action of the human intestine the increase in viscosity reduced the k_{bp} as a consequence of a less well mixed system and an increase in the boundary layer. At concentrations of guar above 0.5% all the biopolymer side mass transfer coefficients are the same.

This novel model of the small intestine has been used to understand how structuring model foods impacts on nutrient delivery to the intestinal wall. The influence that segmentation has on the biopolymer side mass transfer coefficient has been shown to reduce as the amount of guar gum is increased. The results give an understanding of the observations found by Blackburn and co-workers¹⁰ who showed the reduction in the rate of glucose absorption in the humans given model foods containing biopolymers. The SIM can be used to understand further how food ingredients affect the physical and chemical processes of digestion and absorption from the small intestine.

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