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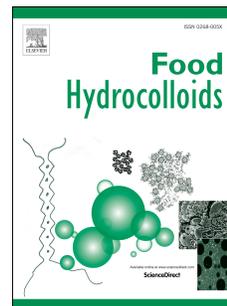
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Hydrocolloids in human digestion: Dynamic *in-vitro* assessment of the effect of food formulation on mass transfer

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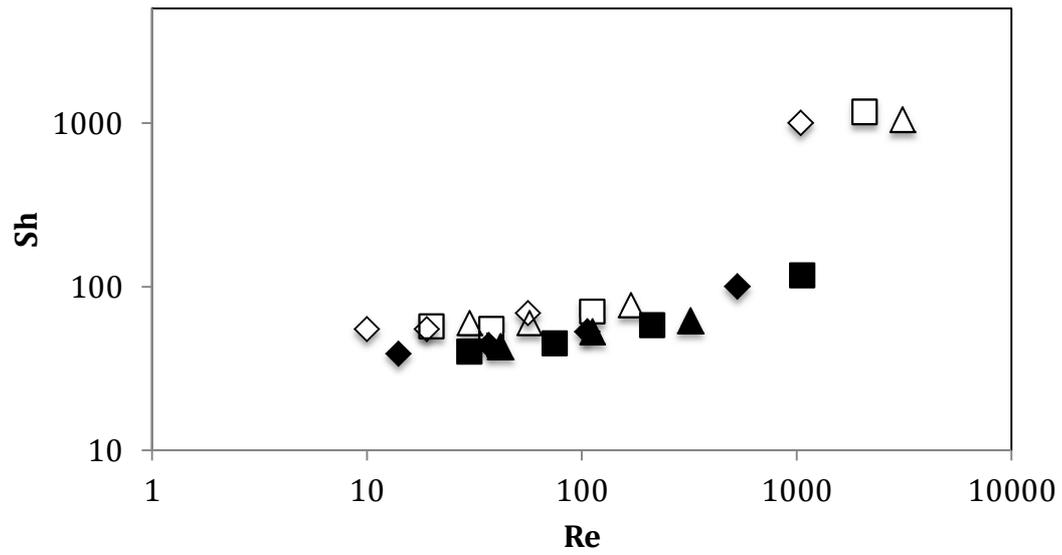
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An increasing Reynolds number (i.e decreasing viscosity) results in an increase of observed mass transfer coefficient

1 **Hydrocolloids in human digestion: Dynamic *in-vitro* assessment of the**
2 **effect of food formulation on mass transfer**

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27 **Abstract**

28 Over the last decade the effect of food formulation on digestion in healthy adults has
29 increasingly gained interest within the scientific community. The area requires
30 multidisciplinary skills from a wide range of fields including medical, chemical, and
31 engineering. In this work, we aim to develop simplified *in-vitro* intestinal models to study the
32 effect of mass transfer on food digestibility and nutrient bioaccessibility for a range of food
33 hydrocolloids. The models developed aim to mimic intestinal motility and focus on describing
34 phenomena occurring during digestion in the mm scale. Results indicate that hydrocolloids
35 have a significant effect in retarding simulated glucose accessibility, and the effects are
36 seemingly more pronounced (fivefold reduction in mass transfer and simulated glucose
37 absorption) at viscosities around 0.01Pa s. This indicates the potential to modulate glucose
38 availability by food formulation.

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40 1. Introduction

41 It is estimated that the food sector is currently responsible for one third (of a \$15 million total
42 market) of hydrocolloid applications worldwide [Seisun 2012]. Although primarily used as
43 texturing agents [Dickinson 2003; 2009; Saha & Bhattacharya, 2010; Funami 2011; Ramirez,
44 Uresti, & Velazquez, 2011], food hydrocolloids are increasingly being associated with a
45 number of important health benefits, including glycaemic and insulinaemic control in type-2
46 diabetes, weight management, and cardiovascular disease prevention [Jenkins, Wolever,
47 Leeds, Gassull, Haisman, Kilawari, Goff, Metz, & Alberti, 1978; Slavin 2005; Edwards & Garcia
48 2009; Dettmar, Strugala, Richardson, & 2011; Kendall, Esfahani, & Jenkins, 2010; Mills,
49 Spyropoulos, Norton, & Bakalis, 2011; Norton, Cox, & Spyropoulos, 2011; Gidley 2013;
50 Fiszman & Varela 2013; Bradbeer, Hancocks, Spyropoulos, & Norton, 2014]. These
51 functionalities are typically linked with the thickening, gelling, water sequestering, and
52 prebiotic properties of food hydrocolloids and their effect on food digestion [Doublier &
53 Cuvelier 2006; Edwards & Garcia 2009; Douaire & Norton 2013]. A possible mechanism of
54 action involves the resistance in mass transfer in the gut in the presence of hydrocolloids due
55 to the increased viscosity of the digested food. This may result in slower gastric emptying and
56 modulated nutrient absorption. However, the detailed mechanisms affecting nutrient
57 bioaccessibility and in particular the impact of hydrocolloids on mass transfer and food
58 digestion are currently not well understood [Gidley 2013; Fiszman & Varela 2013].

59 Quantifying human digestion is a challenging research area. Although the importance of
60 “artificial digestion” has long been appreciated [Sheridan Lea 1890], it is in the last decade
61 that there has been a significant increase in the use of *in-vitro* techniques [Guerra, Etienne-
62 Mesmin, Livrelli, Denis, Blanquet-Diot, & Alric, 2012; Hur, Lim, Decker, & McClements, 2011;
63 Woolnough, Morno, Brennan, & Bird, 2008]. *In-vitro* systems have been broadly classified into
64 ‘batch’ and ‘dynamic’, depending on whether the temporal profile of *in-vivo* digestion (e.g.
65 fluid mixing, addition of simulated gut secretions and the removal of resulting digestion
66 products) is taken into account [Vieira,, Kirby, Ragueneau-Majlessi, Galetin, Chien, Einolf,
67 Fahmi, Fischer, Fretland, Grime, Hall, Higgs, Plowchalk, Ridley, Seibert, Skordos, Snoeys,
68 Venkatakrisnan, Waterhouse, Obach, Berglund, Zhang, Zhao, Reynolds, & Huang, 2013;
69 Guerra *et al.*, 2012; Thomas, Herouet-Guichenev, Ladics, Bannon, Cockburn, Crevel,
70 Fit’Patrick, Mills, Privalle, & Vieths, 2007]. The typical ‘batch’ model consists of a series of
71 vessels, each of which simulates the digestive conditions (e.g. pH, enzymes, temperature,

72 biosurfactants, etc.) in different regions of the gut (e.g. mouth, stomach, small intestine, and
73 colon). Such systems have been used by Englyst, Veenstra, & Hudson [1996] to measure the
74 rapidly available glucose in plant foods and by Oomen, Tolls, Sips, & Van den Hoop [2003] to
75 assess the metabolism of lead into the digestive tract. Similar systems also include the
76 multiple-step pH-stat method that simulates a four-step digestion (oral, gastric, small, and
77 large intestinal phases) [McClements & Li, 2010] and De Boever, Deplancke & Verstraete's
78 [2000] five-step digestive model consisting of five double-jacketed vessels. Although these
79 models provide valuable information, they do not account for actions of the mechanical forces,
80 flow and mixing that might have an effect on the digestion kinetics.

81 Models with dynamic elements are typically application specific, and may include oral, gastric,
82 or intestinal digestion. Oral digestion is complex and difficult to mimic [Le Reverend, Gouseti,
83 & Bakalis, 2013]. Many investigators simplify this step and use commercial meat mincers to
84 simulate oral processing [Bornhorst & Singh 2013; Hoebler, Lecannu, Belleville, Deneaux,
85 Popineau, & Barry, 2002]. Others have developed models to study the effect of chewing
86 [Salles, Tarrega, Mielle, Paratray, Gorria, Liaboef, & Liodenot, 2007], tongue action
87 [Benjamin, Silcock, Beauchamp, Buettner, & Everett, 2012; Benjamin, Silcock, Kieser, Waddell,
88 Swain, & Everett, 2012], shearing [Lvova, Denis, Barra, Mielle, Salles, Vergoignan, Di Natale,
89 Paolesse, Temple-Boyer, & Feron, 2012] and compression [De Loubens, Panouille, Saint-Eve,
90 Deleris, Trelea, & Souchon, 2011; Mills *et al.*, 2011] on oral digestion.

91 Dynamic gastric digestion models typically consider mechanical mixing of the bolus alongside
92 choosing the required physiological conditions (pH, mixing and flow, enzyme concentrations,
93 etc.). In the model of Kong and Singh [2008] mixing is achieved by the motion of small plastic
94 beads, which provide the required mechanical stresses on the food samples. In Chen, Gaikwad,
95 Holmes, Murray, Povey, Wang, & Zhag's [2011] model, mixing is generated using a spherical
96 probe with controlled vertical movement, positioned in the axial centre of a jacketed vessel.
97 The Dynamic Gastric Model (DGM), an apparatus that simulates gastric digestion using a
98 conical flexible walled vessel and a cylinder that processes the food at representative shear
99 rates, has recently been developed at the Institute of Food Research in Norwich UK [Lo Curto,
100 Pitino, Mandalari, Daintry, Fauls, & Wickham, 2011; Mercuri, Lo Curto, Wickham, Craig, &
101 Barker, 2008; Vardakou, Mercuri, Barker, Craig, Faulks, & Wickham, 2011; Wickham & Faulks
102 2012]. The DGM replicates the physical mixing, transit and breakdown forces in the stomach,
103 as well as the relevant physiological conditions (pH gradient and enzymes).

104 Intestinal models in which mixing conditions (segmentation and peristalsis) are an integral
105 part of the process are scarce in the literature. One such model has been reported by
106 Tharakan, Rayment, Fryer, & Norton [2007] and Tharakan, Norton, Fryer, & Bakalis [2010],
107 where segmentation is simulated by squeezing the flexible dialysis tube used to represent the
108 gut wall with the aid of two pneumatically controlled rubber cuffs. In this model, flow
109 conditions have shown to significantly affect simulated absorption rates of chemicals in water
110 as well as in guar gum solutions. The flow characteristics of a shear thinning fluid during
111 simulated peristaltic motion (squeezing of an elastic tube) have been experimentally
112 investigated by Nahar, Jeelani, & Windhab [2012].

113 In the mid-1990s, TNO in the Netherlands introduced TNO intestinal model (TIM), a
114 computer-controlled *in-vitro* digestive system, which represents the different sections of the
115 digestive tract (stomach, duodenum, jejunum, ileum, and colon) using different compartments
116 [Blanquet, Marol-Bonnin, Beyssac, Pompon, Renead, & Alric, 2001; Marteau, Minekus,
117 Havenaar, & Huis in't Veld, 1997; Minekus, Marteau, Havenaar, & Huisintveld,, 1995; Minekus,
118 Smeets-Peeters, Bernalier, Marol-Bonnin, Havenaar, Marteau, Alric, Fonty, & Huis in't Veld,,
119 1999]. Each compartment is equipped with a flexible membrane where simulated digestion
120 takes place, and two outer glass jackets that allow for both temperature and pressure control.
121 Today, two TIM models exist: TIM1 (stomach & small intestine) [Minekus *et al.*1995; Marteau
122 *et al.* 1997] and TIM2 (large intestine) [Minekus *et al.* 1999; Blanquet *et al.* 2001].

123 Models with both 'batch' and 'dynamic' elements have also been described in the literature.
124 For example, 'batch' gastric digestion has been combined with dialysis membranes in cell
125 wells [Argyri, Birba, Miller, Komaitis, & Kapsokfalou, 2009; Argyri, Theophanidi, Kapna,
126 Staikidou, Pounis, Komaitis, Georgiou, & Kapsokfalou, 2011] or dialysis bags [Bouayed,
127 Deuber, Hoffmann, & Bohn, 2012] to simulate absorption of chemicals through the small
128 intestinal wall. In some other systems, peristaltic pumps have been used to control flow of
129 digested foods and related secretions for adults [Mainville, Arcand, & Farnworth, 2005;
130 Savalle, Miranda, & Pelissier, 1989] and infants [Menard, Cattenoz, Guillemin, Souchon,
131 Deglaire, Dupont, & Picque, 2014].

132 Overall, there is evidence that the dynamic nature of human digestion is important in
133 determining digestibility of foods. In particular, flow and mixing in the gut may significantly
134 affect digestive processes, however the link between mass transfer and food digestion is still a

135 largely unexplored area. In this framework, we have developed *in-vitro* models that simulate
136 gut wall contractions with the aim to investigate the effect of gut motility on the accessibility
137 of glucose from model solutions, using a range of food hydrocolloids (guar gum, CMC, pectin).
138 We have analysed our data using engineering principles and dimensionless numbers that
139 characterise the flow (Reynolds number) and mass transfer (Sherwood number) in the gut.
140 We have found that irrespective of the hydrocolloid used or the segmentation patterns
141 applied, the relationship between Reynolds and Sherwood numbers of all investigated
142 digestive conditions and for all model chyme solutions superimposes to a single line. As
143 Reynolds number increased and the flow became less laminar, mass transfer was enhanced.
144 The transition of flow regime was observed at solutions with viscosities of the order of 0.1Pa
145 s, which correlates well with results reported by Tharakan *et al.* [2010]. This viscosity value is
146 within the range of luminal viscosities reported from animal studies [Ellis, Roberts, Low, &
147 Morgan, 1995]. Systems with lower viscosities (higher Reynolds number) showed enhanced
148 mass transfer levels. It is noted that guar gum is a commonly used, relatively inexpensive
149 (\$0.83/lb; \$1.83/kg [Seisun 2012]) and highly acceptable by consumers [Varela & Fiszman
150 2013] hydrocolloid, which has been shown to reduce postprandial blood glucose levels *in-vivo*
151 [Jenkins et al. 1978].

152

153 2. MATERIALS AND METHODS

154 2.1 Sample preparation

155 Model 1% wt/vol (55mM) glucose (D-(+)-glucose by Sigma-Aldrich, UK) solutions of different
156 viscosities were used in this study to evaluate the effect of mass transfer in simulated glucose
157 absorption. This concentration approximates the glucose content of a cup of coffee with half a
158 sachet of sugar added and it is 10 times higher than the homeostatic blood glucose levels.
159 Viscosity was adjusted by addition of different hydrocolloids (guar gum, pectin,
160 carboxymethyl cellulose (CMC)). Distilled water was used in all experiments. Guar gum
161 (105008, ICN Biomedicals, USA for the SIM experiments and Sigma-Aldrich, UK for the DDuo
162 experiments) and pectin (degree of esterification 7680) by Fluka, UK were added slowly into
163 stirred glucose solutions and heated to 80°C for 5min. CMC (Sigma-Aldrich, UK, C5013) was
164 also added slowly into stirred glucose solutions but was more moderately heated (60°C for
165 10min). Mixtures were left to fully hydrate overnight at room temperature under mixing with

166 an overhead stirrer and were further used within 24h. Viscosity was measured using
167 rotational rheometer with cone/plate geometry prior to the experiments (Figure 1).

168 **2.2 *In-vitro* Models: SIM and DDuo**

169 **2.2.1 Model description**

170 The Small Intestinal Model (SIM) used in this work has been developed at the School of
171 Chemical Engineering, University of Birmingham and has been described in detail elsewhere
172 [Tharakan 2008; Jaime Fonseca 2011]. The model (schematic of Figure 2) consists of an inner
173 dialysis tube (Spectre/Por 7®, MWCO 8kDa) that represents the intestinal lumen (diameter of
174 32mm, characteristic of the average adult human small intestine [Schmutz, Le Pennec, Dede, &
175 Perdriel, 2005]), and an outer, concentric, impermeable silicone tube (Flexible Hose supplies,
176 UK, 50mm diameter, 3mm thickness) that borders the outer (recipient) zone. Large pore size
177 (8kDa) was selected to minimise the resistance of mass transfer incurred by the membrane. In
178 a typical experiment, chyme enters from one end of the lumen (feed) and may recirculate with
179 the aid of a peristaltic pump. The recipient fluid (initially distilled water) is also re-circulating
180 and passes through a collection jar, which allows sampling as required. Gut motility is
181 simulated by the pneumatically controlled inflating-deflating motion of two rubber cuffs. Cuff
182 inflation causes squeezing of the tubes, which simulates gut wall contractions. Deflation
183 releases the squeezing pressure and allows the tubes to retrieve their initial cylindrical shape.
184 In the present work, 1% wt/vol (55mM) glucose solutions with or without the addition of
185 hydrocolloids (guar gum, CMC, pectin) were used as model 'chyme' systems and the glucose
186 collected in the recipient zone was measured (DNS method, section 2.3) over time.

187 A second, improved *in-vitro* model (Dynamic Duodenum, DDuo) has recently been developed
188 and initial results are also presented here. The new model implements a more automated and
189 flexible design, with the aim to allow for a more systematic investigation of the effect of
190 peristaltic and segmentation motions on digestion. The DDuo (schematic of Figure 3) uses the
191 same twin tube concept as the SIM, where the small active chemical passes through the pores
192 of a dialysis membrane from the chyme (lumen) to the recipient zone. A fixed secretions port
193 designed for injection of intestinal secretions (such as pancreatic and hepatic fluids) is located
194 100mm away from the feeding end. This is representative of the average distance between the
195 pylorus and the emptying of the pancreatic duct (at the major duodenal papilla) in humans
196 [Kong, Kim, Hyun, Cho, Keum, Jeon, Lee, Chun, Um, Lee, Choi, Kim, Ryu, & Hyun, 2006].

197 Segmentation and peristaltic motions are achieved by squeezing of the membrane at 8
198 independently controlled segmenting positions.

199 It is noted that the models have been specifically designed for studying engineering aspects
200 (mass transfer) of human digestion, which is scarce in the open literature. So far, the effects of
201 other physiological conditions, such as nutrient transportation through the gut membrane or
202 feedback mechanisms, are not represented.

203 **2.2.2. Methods**

204 Unless otherwise stated, the two cuffs of the SIM operated in sequence (one after the other),
205 in cycles of 6s (2s inflation time, 2s deflation time, 2s delay time), performing 10 cycles per
206 minute (cpm) in total. The effect of mixing (segmentation / no segmentation) on simulated
207 glucose absorption was studied for the systems detailed Table 1 (zero-shear viscosity also
208 shown). The ends of the dialysis tubing were closed and no chyme recirculation occurred
209 (closed configuration). Experiments were conducted in triplicates and the average with error
210 bars is shown in the graphs.

211 The effect of segmentation frequency on simulated glucose absorption was studied for the
212 systems detailed in Table 2 using the open configuration, where chyme re-circulated at
213 $1.6 \times 10^{-4} \text{ m}^3 \text{ s}^{-1}$ with the aid of a peristaltic pump. Cuffs operated at cycles of 3s, 6s, and 9s with
214 equal inflation, deflation, delay intervals of 1s (20cpm), 2s (10cpm) and 3s (5cpm),
215 respectively. Glucose increase in the recipient zone was determined using the DNS method,
216 described in section 2.3. Experiments were conducted in triplicates and the average with
217 error bars is shown in the graphs.

218 Initial experiments with the DDuo were performed using 1% w/w glucose solutions with or
219 without addition of 1% guar gum as model chyme systems. Unless otherwise stated,
220 segmentation occurred at 4 positions (blue arrows in Figure 3), alternating (with the black
221 arrows in Figure 3) every 10s. Although further work is required for conclusions to be
222 reached, initial results are included here to indicate the potential of the new model and how it
223 compares with the SIM.

224 **2.3 Sample analysis: DNS**

225 Samples from the recipient side were analysed using the dinitrosalicylic acid (DNS) method
226 for reducing sugars [Jaime-Fonseca, 2011; Miller 1959]. Equal volumes (1mL) of sample (or

227 water as reference system) and DNS reagent (0.1% dinitrosalicylic acid; 30% w/w potassium
 228 sodium tartrate; 0.4M NaOH) were added in a test tube, mixed, and placed in boiling water for
 229 5min. The resultant products were immediately cooled to room temperature and measured
 230 spectrophotometrically at 540nm.

231 2.4. Data analysis

232 2.4.1 Mass Transfer Coefficients

233 Mass transfer coefficients were determined as described previously [Tharakan *et al.*, 2007;
 234 Tharakan *et al.*, 2010; Jaime-Fonseca, 2011]. A typical graph of glucose absorption in the
 235 recipient zone over time is shown in Figure 4 and is used to estimate mass transfer in the
 236 model gut. The molar flux across the membrane is calculated using equations 1 and 2. The
 237 overall mass transfer coefficient ($K_{overall}$) is then obtained from equation 3.

238

$$239 \quad A = 2 \cdot \pi \cdot r \cdot L \quad (1)$$

$$240 \quad M_T = \frac{\text{mol}_{\text{glucose}}}{A \cdot t} \quad (2)$$

$$241 \quad K_{overall} = \frac{M}{\Delta C} \quad (3)$$

242

243 where r is the membrane radius (m), L is the length (m), A is the total absorbing surface area
 244 (m^2), $\text{mol}_{\text{glucose}}$ is the glucose in the recipient side (mol), M_T the total molar flux ($\text{mol m}^{-2}\text{s}^{-1}$),
 245 ΔC is the concentration difference (mol m^{-3}) between the two sides of the membrane (taken as
 246 the initial concentration difference of 0.055M, assumed to change insignificantly within the
 247 experimental time), and $K_{overall}$ is the overall mass transfer coefficient (m s^{-1}).

248 Detection of a glucose molecule requires transportation from the lumen to the dialysis
 249 membrane, passing through the membrane, and transfer to the recipient fluid. This three-
 250 stage process is characterised by the luminal mass transfer coefficient, (K_{lumen} , m s^{-1}), diffusion
 251 (described by coefficient D_{membrane} , $\text{m}^2 \text{s}^{-1}$) through the membrane of thickness Z_{membrane} (m),
 252 and the recipient side's mass transfer coefficient (K_{rec} , m s^{-1}). Equation 4 gives the relationship
 253 between the local and overall transfer coefficients (K_{system} is the combined mass transfer
 254 through the membrane and the recipient zone, m s^{-1}).

255

$$256 \quad \frac{1}{K_{overall}} = \frac{1}{K_{lumen}} + \frac{Z_{\text{membrane}}}{D_{\text{membrane}}} + \frac{1}{K_{rec}} = \frac{1}{K_{lumen}} + \frac{1}{K_{\text{system}}} \quad (4)$$

257
 258 To determine K_{lumen} of the investigated chyme samples, it is first necessary to estimate K_{system} ,
 259 which is assumed constant for all the experiments. This was achieved from experiments that
 260 minimise resistance to mass transfer at the lumen side (maximise K_{lumen}), so that $1/K_{\text{lumen}}$
 261 would be much smaller than $1/K_{\text{system}}$. To minimise resistance in the luminal side, an
 262 increasing flow rate was applied in the inner tube, which was filled with 1% glucose in water
 263 until no significant increase in K_{overall} was observed. This value (estimated at $5.3 \times 10^{-7} \text{ m s}^{-1}$,
 264 Tharakan, 2008) was taken as K_{system} .

265 2.4.2 Reynolds and Sherwood numbers

266 The dimensionless Reynolds (Re) and Sherwood (Sh) numbers were estimated from
 267 equations 5 and 6, to further characterise mass transfer and study the relative importance of
 268 convective and diffusive processes in the model gut.

269

$$270 \quad Re = \frac{\rho u(2r)}{\mu} \quad (5)$$

$$271 \quad Sh = \frac{K_{\text{lumen}} r}{D_{\text{glucose}}} \quad (6)$$

272
 273 where ρ is the density of the fluid (kg m^{-3}), u is the velocity of the fluid (m s^{-1}), r is the radius of
 274 the membrane (m), μ is the viscosity of the solution (Pa s), D_{glucose} is the diffusion coefficient of
 275 glucose ($6.9 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$). The velocity value used for u was estimated as follows. Each cuff
 276 contraction was assumed to displace fluid of volume equal to the volume of a cylinder with
 277 diameter $2r$ (the diameter of the membrane) and length L_{cuff} , the length of each rubber cuff.
 278 This was divided by the inflation time to calculate the volumetric flow rate, which was then
 279 divided with the cross sectional area of the membrane to obtain the velocity value.

280 3. RESULTS

281 3.1 Mass transfer in the SIM

282 Simulated glucose absorption from 1% glucose in aqueous, guar gum (0.1%), and CMC (0.1%
 283 and 0.5%) solutions with and without segmentation showed linear curves of the shape of
 284 figure 4 without any plateaus (no lag time or converge limit, data not shown). The relevant
 285 overall mass transfer coefficients were calculated from equation 3, and results are shown in
 286 Figure 5 as a function of zero-shear viscosities. Figure 5 demonstrates increased glucose

287 absorption with application of segmentation movements, which can be attributed to enhanced
288 mass transfer to the membrane wall due to the squeezing motions of the cuffs. The effect was
289 more profound for the aqueous solution, where application of segmentation resulted in 30%
290 increase in mass transfer coefficient. More viscous solutions of 0.1% guar gum and 0.1% CMC
291 solutions showed maximum 20% increase in K_{overall} on application of squeezing movements.
292 This is in good agreement with Tharakan et al. [2007; 2010], who reported reduced effect of
293 squeezing on mass transfer as viscosity increased. Figure 5 also indicates maximum overall
294 mass transfer coefficient for the lowest viscosity fluid on application of segmentation
295 movements, suggesting that at low viscosities there is minimal resistance to mass transfer.
296 Increasing chyme viscosity (above 2mPa s) resulted in reduction of mass transfer (by 15%
297 and 90% as viscosity increased from 1 to 20 and 200Pa s, respectively). Interestingly, at 0.5%
298 CMC (200mPa s zero viscosity), glucose transport to the recipient zone was practically
299 inhibited without segmentation within the timescale of the experiments.

300 These results correlate well with estimated K_{overall} from *in-vivo* data of human volunteers who
301 consumed an oral glucose dose (250mL of 10% by weight glucose drink) with or without
302 3.6% wt/vol guar gum [Blackburn, Redfem, Jarjis, Holgate, Hanning, Scarpello, Johnson, &
303 Read, 1984]. Although glucose and guar gum concentrations were different to those used in
304 the present work, it is encouraging to notice that both the present and the *in-vivo* data
305 resulted in K_{overall} of the same order of magnitude (for aqueous solutions 5.35×10^{-7} and
306 5.47×10^{-7} m/s, respectively) and that addition of the hydrocolloid prompted reduction of
307 K_{overall} (from 5.47×10^{-7} to 2.91×10^{-7} m/s). The effect of guar gum in reducing postprandial
308 glucose levels was attributed to the inhibiting action on fluid convection by the intestinal
309 motility due to increased chyme viscosity.

310 Figure 6 shows the effect of segmentation frequency on mass transfer for guar gum and pectin
311 solutions. For all investigated conditions, increasing the viscosity resulted in a decrease in
312 mass transfer. Guar gum and pectin systems showed similar trends: an approximately
313 threefold reduction in K_{overall} was observed as zero shear viscosity increased from 0.02 Pa s to
314 1.2 Pa s in systems containing guar gum (0.25% and 0.63%, respectively) and from 0.05Pa s to
315 1.9Pa s in pectin systems (10% and 30%, respectively). For the same systems, the effect of
316 segmentation frequency was found marginal and similar overall mass transfer coefficients
317 were estimated for all investigated protocols. Further increase in guar gum concentration (to

318 0.75%) had an insignificant effect on mass transfer, in agreement with previous work
319 reported by Tharakan *et al.* [2007; 2010].

320 Interestingly, increased frequency of segmentation contractions (i.e. faster squeezing of the
321 membrane) is expected to result in increased mixing and therefore higher mass transfer
322 coefficients. It may also further enhance mass transfer by decreasing the “unstirred water”
323 layer adjacent to the gut wall, which further obstructs molecular diffusion and nutrient
324 absorption [Doublier & Couvelier 2006]. Similar conclusions would be made according to the
325 ‘surface-renewal’ theory [Cussler 2000]. However, frequency of contractions did not have a
326 significant effect on the estimated K_{overall} for both guar gum and pectin solutions in all
327 investigated concentrations. It is possible that the time scale of the perturbations induced by
328 the squeezing motions of the cuffs is smaller than the relaxation time of the system under
329 investigation. Any changes in the squeezing frequency would then be expected to have
330 marginal effect on mass transfer. This has been identified as a possible limitation of the SIM
331 and it has been addressed in the next generation (DDuo).

332 Overall figures 5 and 6 demonstrate the potential of both food formulation and segmentation
333 in controlling digestion processes. From those results one could conclude that the effect of
334 formulation on food digestibility is complex and rheological variables other than viscosity
335 may play an important role in determining nutrient bioaccessibility. In addition, food
336 formulation is believed to further impact *in-vivo* segmentation patterns (e.g. liquid foods are
337 said to stimulate deep contractions while highly viscous foods are generally associated with
338 shallow muscle movements) [Jaime-Fonseca, 2011].

339 Figure 7 shows the Reynolds and Sherwood numbers, calculated from equations (5) and (6).
340 As a general trend, convection becomes increasingly more important than diffusion (i.e. Sh
341 number increases) as Re number increases above 100. This indicates that higher Re enhances
342 convective mass transfer. Interestingly, a notable “step” towards convective processes
343 appears in Re numbers in the region of 1000 (low viscosity fluids, of about 20mPa s) for the
344 guar gum solutions. This could be the result of a change of the flow regime from laminar to
345 transitional-turbulent, resulting in increased mixing and mass transfer. At Re numbers below
346 100, the flow becomes fully laminar and an increase of Re does not result in a significant
347 increase of Sh (i.e. convection is not enhanced). The different segmentation patterns appeared
348 to influence the relationship between Sh and Re only marginally.

349 **3.2 Mass transfer in DDuo**

350 Having established that both formulation and mixing conditions are significant in determining
351 mass transfer and nutrient bioaccessibility in the gut, a new model was built with improved
352 functionality and automation, as discussed in section 2.2.1. The new model aims at addressing
353 the limitations observed in the SIM and offers flexibility in reproducing gut motility: there are
354 8 segmentation positions (i.e. squeezing of the porous membrane), each of which is only 1cm
355 long (with respect to the 12cm long cuffs of SIM). The segmentation points can be controlled
356 separately, so that each moves at the required time and rate.

357 Initial data obtained with the DDuo are shown in Figures 8-10. Figure 8 shows the effect of
358 mixing conditions on glucose absorption from 1% glucose in aqueous and 1% guar gum
359 solutions. Mixing was induced by squeezing at alternating positions at either 4 locations
360 (gray/black arrows in Figure 3) or 1 location (positions 2 and 6 in Figure 3). The results are
361 comparable to those obtained from the SIM model. When mixing was reduced to one
362 segmenting point, a delay of 10min was observed for both water and guar gum solutions,
363 before determining glucose in the recipient zone. These results indicate that the way
364 intestinal motility is reproduced in the *in-vitro* models could affect the observed mass transfer
365 coefficient. The results from DDuo indicate that increasing the number of segmentation points
366 can result in a change of accessible glucose indicating an increase of mixing.

367 In Figure 9 the estimated overall mass transfer coefficients are shown for different
368 segmentation points. Results indicate that at 1 segmentation point (i.e. lower mixing) mass
369 transfer was reduced by 25% and 45% for aqueous and guar gum systems, respectively. In
370 addition, the effect of the number of segmentation points was more profound at higher
371 viscosity mixing (40% reduction of K_{overall} for the 1% guar gum) when compared to low
372 viscosity (only 15% reduction on water).

373 Figure 10 shows the effect of mixing frequency (at 4 segmentation points) on K_{overall} from 1%
374 glucose in aqueous and 1% guar gum systems. Results indicate that under investigated
375 conditions, increased segmentation frequency appears to enhance mass transfer. On all
376 occasions, the lower viscosity fluid resulted in higher (up to 30%) mass transfer. However, at
377 12cpm it appears that the difference between the aqueous and viscous systems was marginal
378 (<10%), indicating a nearly homogeneous mixing. Overall, Figures 8 - 10 demonstrate the
379 flexibility of DDuo and its potential as a more adaptable tool to understand the effect of

380 intestinal motility on glucose bioaccessibility. Further work is required to obtain an
381 understanding of the detailed effect of gut motility on mass transfer and food digestibility.

382 4. CONCLUSIONS

383 There is a growing interest in controlling the nutritional values of foods using hydrocolloids. A
384 mechanism of slowing glucose bioaccessibility has been attributed to reduction in mass
385 transfer through the gastrointestinal tract. This work presents *in-vitro* digestion studies using
386 novel models with the ability to simulate intestinal motility, and illustrates the importance of
387 mass transfer on simulated glucose absorption by using a range of food hydrocolloids. The
388 models simulate flow and mixing in the gut. Addition of guar gum, CMC, and pectin showed
389 reduction of glucose bioaccessibility by up to 30% compared with aqueous solutions *in-vitro*.
390 Further work is required to understand if this reduction of mass transfer could result
391 in/explain the significant delay of *in-vivo* post-prandial blood glucose observed by the
392 addition of hydrocolloids. Overall, obtained results indicate that the effects of hydrocolloids
393 on simulated digestibility are complex and for investigated hydrocolloid systems/conditions,
394 increasing viscosity appeared to reduce mass transfer coefficients. This implies the potential
395 of designing healthier foods by engineering the viscosity of the digested food.

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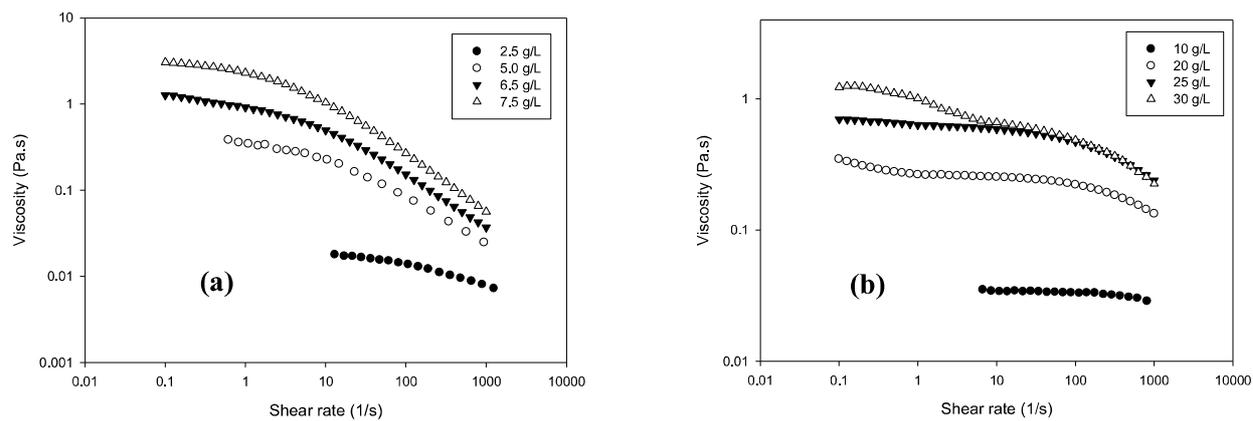
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590 Figure 1: Shear viscosity of solutions (with concentrations) used in the experiments: (a) guar
591 gum; (b) pectin.
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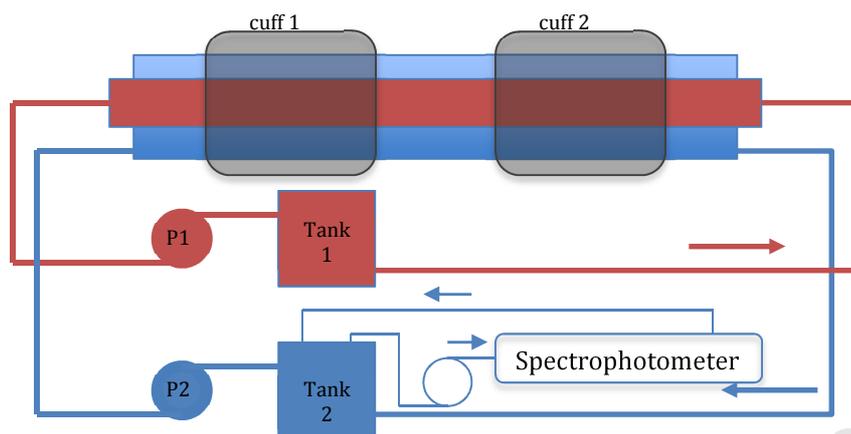
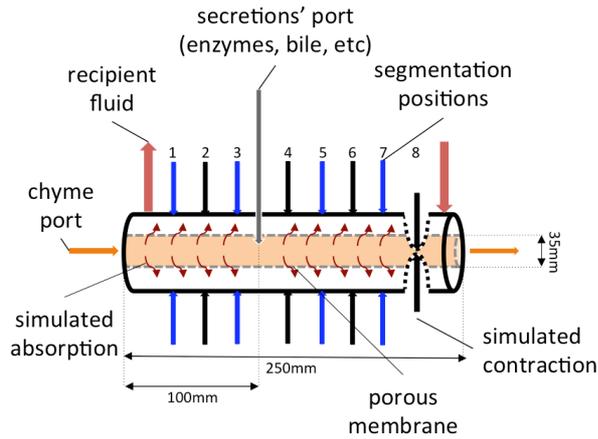


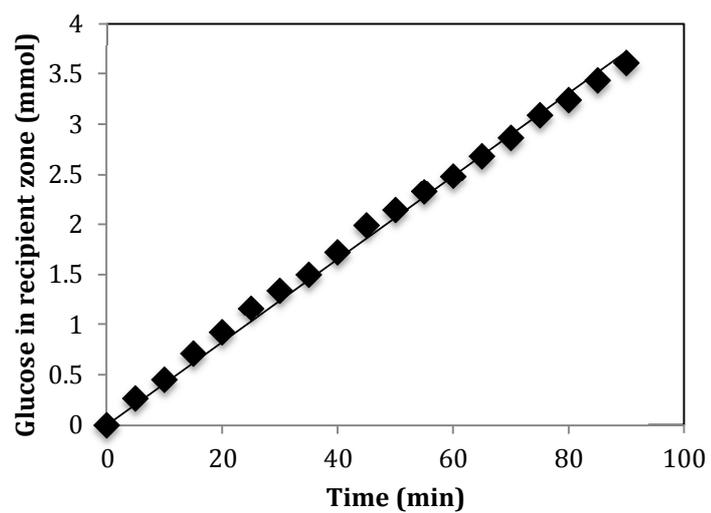
Figure 2: Schematic drawing of Small Intestinal Model (SIM). The investigated (red colour) and recipient (blue colour, initially water) fluids recirculate in the luminal and recipient sides of the model respectively, using peristaltic pumps P1 and P2. Segmentation is mimicked by squeezing the tubes radially, using two pneumatically controlled rubber cuffs (cuff 1 and cuff 2). The active compound passes through the porous inner membrane from the luminal to the recipient side, where it is quantified spectrophotometrically.



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Figure 3: Schematic of Dynamic Duodenal Model (DDuo). The investigated fluid (orange coloured here for clarity) enters the luminal side of a porous membrane used to simulate intestinal wall. The recipient side is bordered by a non-permeable silicone tube. Enzymes and other secretions are injected through the secretions port, located at 100mm distance from the chyme entrance to represent physiological conditions. Segmentation and peristaltic movements are simulated by applying pressure at the membrane at 8 possible positions.

Motion can be controlled independently.

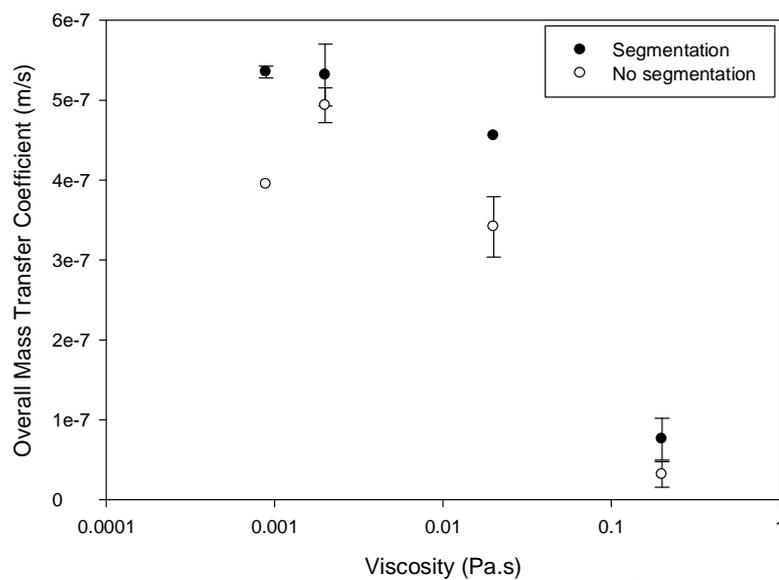


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624 Figure 4: Typical plot of absorbed glucose in the recipient zone versus time (from 1% aqueous
625 glucose solution).

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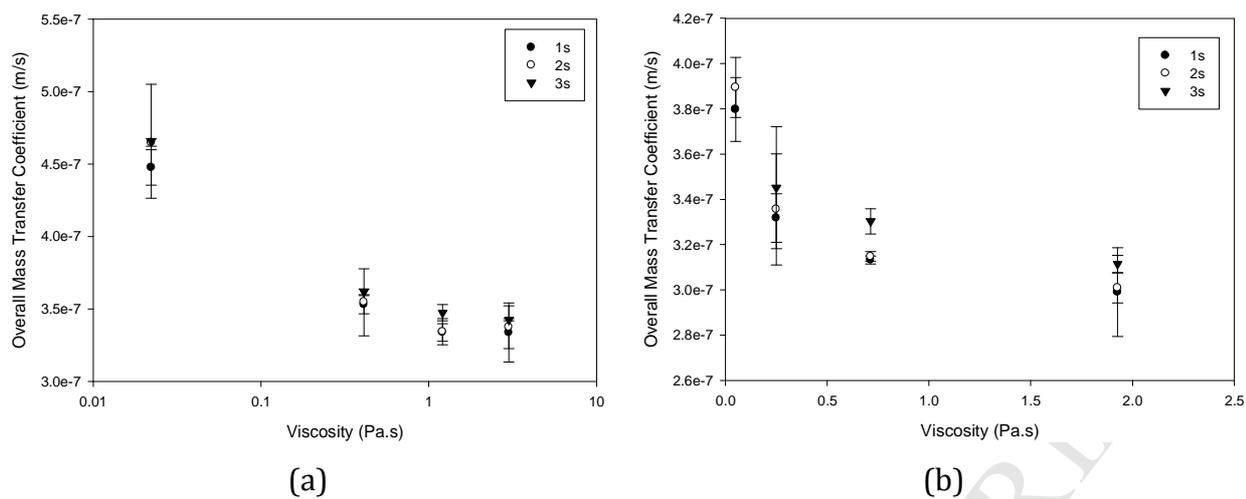
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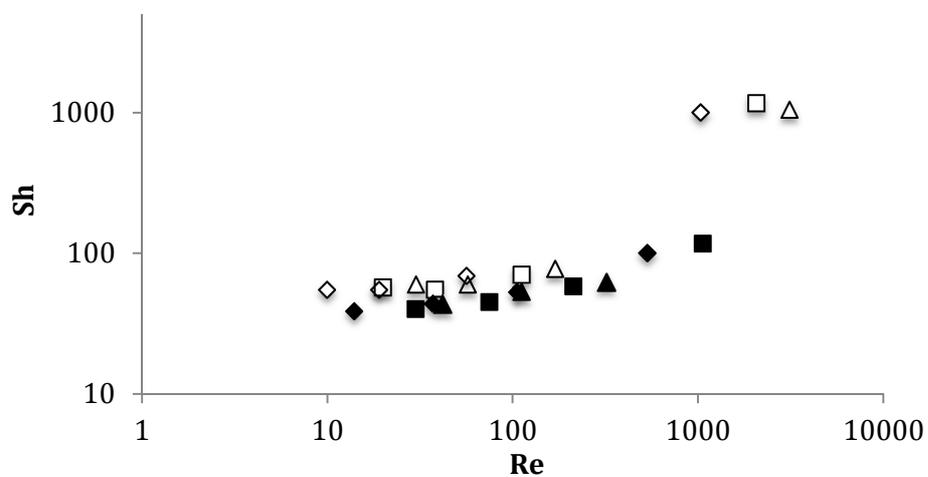
Figure 5: Overall Mass Transfer Coefficient with and without segmentation for systems of different zero-shear viscosities.



631 Figure 6: Effect of segmentation frequency on overall mass transfer rate from 1% glucose in
632 (a) guar gum; (b) pectin solutions of different zero-shear viscosities.
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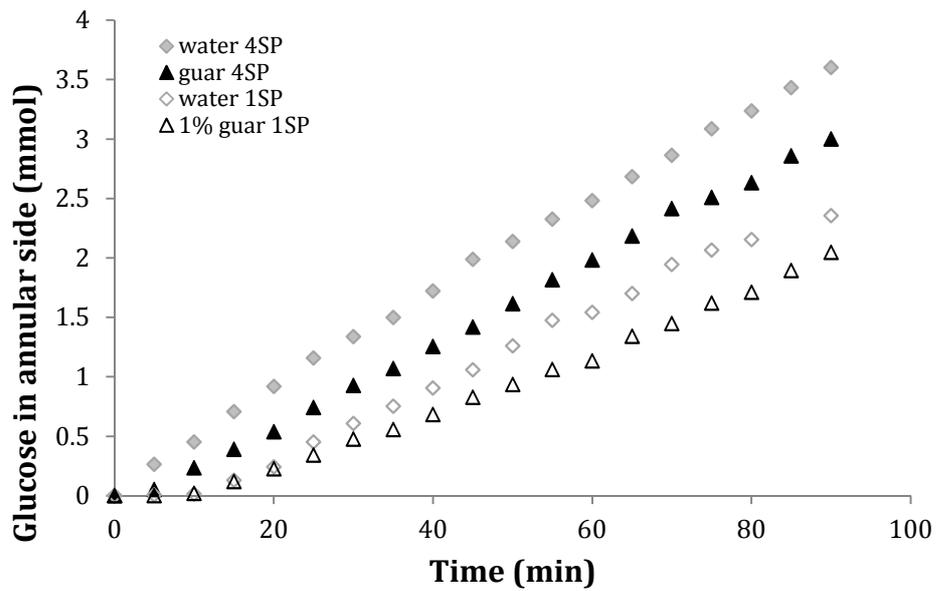
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638 Figure 7: Correlation between Sherwood (Sh) and Reynolds (Re) numbers for guar gum
639 (white symbols) and pectin (black symbols) solutions at high (1s, rhombus), medium (2s,
640 squares), and low (3s, triangles) mixing.

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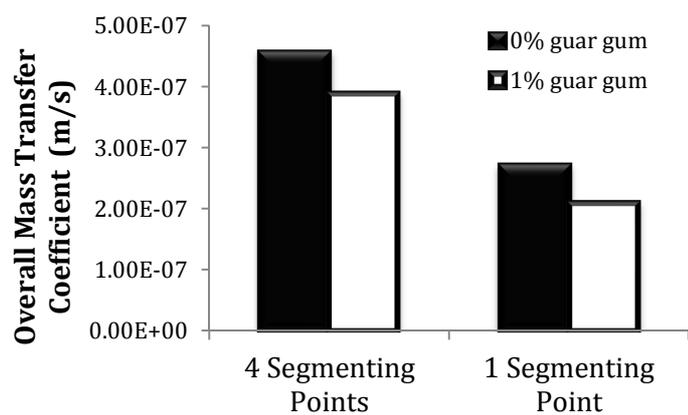
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Figure 8: Simulated glucose absorption at high (4 segmenting positions) and low (1 segmenting position) mixing for 1% glucose in aqueous or 1% guar gum solutions, using Dynamic Duodenal model (DDuo).

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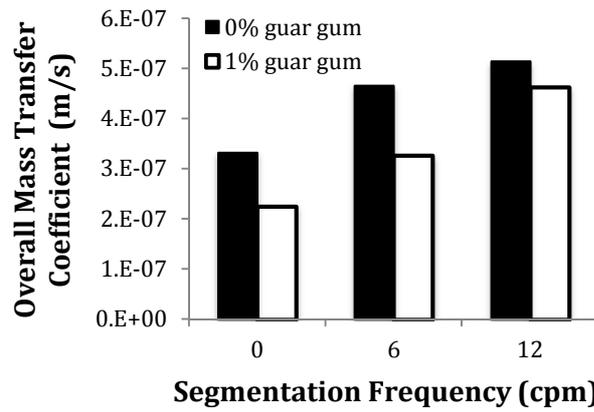
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Figure 9: Overall mass transfer rates associated with the conditions of Figure 9 (initial lag time not considered in the calculations)

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659 Figure 10: Overall mass transfer coefficient in Dynamic Duodenal model (DDuo) for 1%
660 glucose in aqueous and 1% guar gum solutions at different segmentation frequencies (0, 6,
661 and 12cpm)

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666
667 Table 1: Hydrocolloid systems and zero-shear viscosities studied with and without
668 segmentation movements in the Simulated Intestinal Model (SIM) and their respective
669 viscosities.

<i>System</i>	η_0 (mPa s)
aqueous	1.0 ± 0.2
Guar gum 0.1%	2.0 ± 0.4
CMC 0.1%	20.0 ± 0.2
CMC 0.5%	200.0 ± 0.1

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682 Table 2: Hydrocolloid systems and zero-shear viscosities studied under different
683 segmentation patterns in the Simulated Intestinal Model (SIM) (as described in section 2.2.2).

<i>System</i>	<i>Concentration (g/L)</i>	<i>η_0 (Pa s)</i>
Guar gum	2.50	0.0222 ± 0.0018
	5.00	0.4108 ± 0.0296
	6.25	1.2090 ± 0.0961
	7.50	3.192 ± 0.1982
Pectin	10	0.0498 ± 0.0217
	20	0.2530 ± 0.0770
	25	0.7133 ± 0.0607
	30	1.9265 ± 0.1039

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Please find below 5 brief bullet points to convey the core findings of the work.

- Food formulation impacts mass transfer in simulated *in-vitro* model gut
- Flow regime affects mass transfer independently of formulation
- As flow becomes less laminar mass transfer increases in the model gut
- At increased mass transfer simulated glucose absorption is increased
- Preliminary data with improved *in-vitro* model agree with previous observations