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2 **Effect of the rheological properties of the liquid carrier on the *in***  
3 ***vitro* swallowing of Solid Oral Dosage Forms**

4  
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10  
11 **Keywords**

12 Capsule; Tablet; Carrier fluids; Rheology; Shear viscosity; Relaxation time; Dysphagia

13  
14 **Abstract**

15 Solid Oral Dosage Forms (SODF) are the most popular oral drug delivery forms, but they can  
16 be difficult to swallow, especially for patients suffering from swallowing disorders. This study  
17 investigated the dynamics of different combinations of liquid carriers and SODF during the oral  
18 phase of swallowing using an *in vitro* model. The rheological properties of the carriers were  
19 characterized using shear and extensional rheometry, and their effect on bolus velocity, bolus  
20 shape, post-swallow residues, and SODF position within the bolus was evaluated. The latter  
21 has been identified as a novel and promising variable to discriminate between alternative  
22 formulations. When swallowed with water, capsules and tablets did not impact significantly the  
23 velocity of the bolus, but they lagged behind the liquid bolus, suggesting that low viscosity  
24 Newtonian fluids are not efficient carriers for SODF. Increasing the viscosity of the carrier at  
25 high shear rates improved the ability of the liquid to transport the SODF but also increased the  
26 amount of post-swallow residues. At equivalent shear viscosity, elastic and extensional

27 properties of carriers influenced positively the position of the SODF in the bolus. Capsules and  
28 tablets were transported toward the front of these boluses, during the oral phase of swallowing,  
29 which is considered beneficial to avoid SODF sticking to the mucosa in the following stages of  
30 swallowing. Thin elastic liquids appear as an interesting option to promote safe swallowing of  
31 capsules and tablets. Clinical studies are, however, necessary to confirm this positive effect in  
32 healthy and dysphagic patients.

33

## 34 **Introduction**

35 Solid Oral Dosage Forms (SODF), such as powders, granules, tablets and capsules are the  
36 most popular format for adult medications. Heppner et al., (2006) estimated that 65 to 70% of  
37 all medicines prescribed to patients in Germany in 2006 were tablets and capsules, intended  
38 to be swallowed whole. More recently, Schiele et al., (2013) reported that 90.1% of the drugs  
39 mentioned by patients attending general practices were tablets and capsules of different  
40 shapes and sizes.

41 Capsules and tablets remain the most popular oral drug delivery forms in the market because  
42 they are simple to handle, process, and store for industries and patients (Hoag, 2017; Shaikh  
43 et al., 2018). However, it can be challenging to swallow them, which may lead to non-  
44 adherence to prescribed medicine. Medication-related swallowing difficulties affect between  
45 10 and 60 % of the adult population (Fields et al., 2015; Lau et al., 2015; Punzalan et al., 2019;  
46 Schiele et al., 2013; Strachan & Greener, 2005; Tahaineh & Wazaify, 2017), and have probably  
47 been underestimated in the past since people may be reluctant to seek advice from health  
48 professionals regarding such difficulties (Lau et al., 2015).

49 Patients may feel anxious about swallowing tablets and capsules because of anatomical  
50 features related to age and gender (dimensions and function of mouth, pharynx, upper  
51 esophageal sphincter and esophagus, etc.), physical characteristics of the dosage form itself  
52 (dimensions, surface properties, compliance, palatability, color, etc.) (Liu et al., 2016;

53 Radhakrishnan, 2016; Schiele et al., 2013; Shariff et al., 2020), or inappropriate swallowing  
54 techniques (Forough et al., 2018; Schiele et al., 2014). Classical SODF are particularly  
55 troublesome for patients suffering from swallowing disorders (dysphagia), who are at higher  
56 risk for choking and silent aspiration (Schiele et al., 2015). SODF may also stay trapped in the  
57 laryngeal folds and trigger local inflammations, esophagitis and ulcerations (Food and Drug  
58 Administration, 2015).

59 Systematic *in vivo* studies about SODF swallowing are scarce and most of the data available  
60 in the literature focus on the effect of the tablet/capsule characteristics (e.g., size, shape,  
61 density, film coating) on the acceptability of the SODF. Kasashi et al., (2011) reported oral  
62 transit times between 0.95 and 1.45 s for large hard gelatin capsules (19 mm x 7 mm)  
63 swallowed with water by healthy volunteers and evaluated with videofluoroscopy.  
64 Unfortunately the authors did not measure the oral transit time of the bolus without capsules.  
65 Yamamoto et al., (2014) showed that round biconvex tablets (up to 9 mm in diameter) affect  
66 swallowing behaviors in healthy subjects. They reported an increase in the total number of  
67 swallows with increasing tablet size and number, as well as an increase in the EMG activity of  
68 the suprahyoid muscles (burst area and duration) when taking a round biconvex tablet (9 mm  
69 in diameter) compared to the water control. Schiele et al., (2015) showed that the addition of  
70 SODF to fluids or foods worsens the swallowing performances of stroke patients. They  
71 observed an increased risk in penetration and aspiration independently of the type and shape  
72 of the SODF.

73 Dysphagia is associated with various neurological, muscular, and respiratory disorders  
74 (strokes, Alzheimer's and Parkinson's diseases, metabolic myopathies, throat cancers, etc.),  
75 and with age-related physiological changes (Stegemann et al., 2012). Given the current trend  
76 towards population ageing (United Nations, 2020), dysphagia is a growing health concern  
77 which is believed to affect at least 15% of the elderly (Sura et al., 2012). Furthermore, older  
78 adults are commonly prescribed multiple medications to manage multiple comorbidities  
79 (Masnoon et al., 2017), and most hypoglycemic agents, anti-hypertensives, or anti-

80 dyslipidemia drugs are only available in SODF overlooking their special swallowing needs  
81 (Forough et al., 2018; Liu et al., 2016). Consequently, tablets and capsules are often  
82 manipulated by health care professionals or caregivers to facilitate their administration, but this  
83 has been related to an increased number of adverse events and medical errors (Logrippo et  
84 al., 2017; Nissen et al., 2009; Shariff et al., 2020).

85 Aside from drug compounding, other strategies may be used to help people struggling with  
86 tablets and capsules (Patel et al., 2020; Satyanarayana et al., 2011). First, it may be possible  
87 to switch to another type of SODF (i.e., smaller in size, with a different shape or coating,  
88 chewable or orodispersible, etc.), to another pharmaceutical form (liquid or gel formulations,  
89 microparticule, etc.), or to a different route of administration (transdermal delivery for example).  
90 If this is not possible, swallowing assisting devices like cups and straws (Forough et al., 2018)  
91 and lubricant sprays (Diamond & Lavalley, 2010) or coatings (Uloza et al., 2010) have been  
92 developed. Soft foods (puddings, apple sauce, yogurts, etc.) are also frequently used as  
93 swallowing-aid vehicles, but the compatibility between drug products and foods should be first  
94 carefully evaluated (Fukui, 2015).

95 Recently, lubricant gels and thickened liquids specially designed to help swallowing whole  
96 SODF have appeared on the market (“Gloup”, “Slō tablets”, “Medcoat”, or “Magic Jelly” for  
97 example). These products are inspired in products recommended for dysphagia management  
98 and are based on starch or gum-based viscoelastic materials. They are designed to increase  
99 swallowing comfort by masking the taste and transit of the SODF in the mouth and in the throat  
100 during swallowing. They also claim to support a smooth movement of the SODF from the  
101 mouth to the stomach by reducing the risk of adhesion (Fukui, 2015). However, few studies  
102 have been published about those lubricant gels and they are only recommended for people  
103 without dysphagia at the moment (Malouh et al., 2020). Fukui et al., compared water to a  
104 swallowing aid (“Magic Jelly”, composed of agar, carrageenan, sugar, sugar alcohols, and  
105 flavors) used with placebo tablets and capsules (15 to 19 mm in diameter) by a group of 50  
106 healthy people (20 to 50 years old). According to their sensory tests, the jelly was judged to be

107 superior to water, useful, and safe, and their videofluoroscopic swallowing study (VFSS)  
108 revealed that capsules taken with the jelly took only 8 s to reach the stomach against 18 s for  
109 capsules swallowed with water (Fukui, 2004, 2015). (Wright et al., 2019) reported the results  
110 of a phase IV open-label randomized controlled cross-over trial (12 healthy males, aged 18-35  
111 years), comparing aspirin tablets administered with water or encapsulated in a gelatin-based  
112 gel. The gel coating improved the taste and allow the tablet to be swallowed without water, but  
113 the bioavailability of the drug was significantly reduced.

114 Regarding SODF swallowing for patients with dysphagia, (Schiele et al., 2015) reported  
115 promising results from a video-endoscopic evaluation of 52 dysphagic stroke patients who  
116 swallowed medium-sized placebos with water thickened to pudding consistency, or milk: the  
117 prevalence rate of SODF swallowing difficulties was lower with texture-modified water than  
118 with milk. Authors concluded that tablets and capsules should rather be delivered with  
119 semisolids than fluids (Schiele et al., 2015).

120 There is a general agreement that texture modification of liquids using shear thinning food  
121 thickeners promotes safe swallowing and helps managing dysphagia (Newman et al., 2016;  
122 Rofes et al., 2014), but the role of elastic and extensional properties of fluids on the dynamics  
123 of bolus transport has only recently been investigated and is still not fully understood (Hadde  
124 et al., 2019, 2020; Mackley et al., 2013; Sukkar et al., 2018; Nishinari et al., 2019; Marconati  
125 & Ramaioli, 2020; Qazi et al., 2020). In a previous study, we observed that elastic and  
126 extensional properties of thickened liquids play a significant role during bolus ejection from an  
127 *in vitro* oral cavity (Marconati & Ramaioli, 2020). Bolus elongation during *in vitro* swallowing  
128 and post-swallow residues were limited with thin elastic liquids, suggesting a lower risk of  
129 fragmentation *in vivo*. A clinical study by (Hadde et al., 2019) confirmed the effect of  
130 extensional properties on bolus elongation and safety, but no fluid with strong extensional  
131 properties were considered.

132 The objective of this study was to evaluate the effect of the rheology of different liquid carriers  
133 on the oral phase of swallowing of capsules and tablets *in vitro*, and in particular whether the

134 transport of SODF from the oral cavity to the pharynx is facilitated by the use of elastic liquids.  
135 The rheological properties of a selection of liquid carriers were characterized using shear and  
136 extensional rheometry, and *in vitro* swallowing experiments were performed with a capsule or  
137 a tablet in order to explore the swallowing dynamics of different combination of carrier and  
138 SODF.

## 139 **Materials and methods**

### 140 *Materials*

141 This study considered mineral water (Vittel) and five different types of liquid carriers (three  
142 thickener solutions and two model systems). Different concentrations were used for each  
143 carrier with the objective to obtain two categories of fluids, classified as Level 1 and Level 3 to  
144 4 according to the International Dysphagia Diet Standardization Initiative (IDDSI) framework.  
145 Traces of a dye (0.02 % w/w) were added to the samples to enhance image contrast.

146 Oat extract samples (0.3 and 1% w/w) were provided by Nestlé Research (Lausanne, CH).  
147 The frozen oat extract samples were thawed in a refrigerator at 4°C for 18 hours, then left to  
148 equilibrate at ambient temperature for 3 hours, prior to the rheological characterization and *in*  
149 *vitro* tests. In a previous study, these samples were characterized, presenting interesting  
150 elastic properties (Marconati & Ramaioli, 2020).

151 Aqueous suspensions of a commercial xanthan gum based thickener (Resource®  
152 ThickenUp™ Clear, Nestlé Health Science), referred to as TUC in the following text, were also  
153 used. TUC ingredients are the following: maltodextrin (from corn, and potato), xanthan gum,  
154 and potassium chloride. Suspensions with different IDDSI levels were prepared by adding 100  
155 mL of mineral water to 0.6 g, 2.4 g, or 3.6 g of TUC powder, according to the recommendations  
156 of the supplier. TUC is commonly used in the management of dysphagia and was used as an  
157 example of commercial texture modifier, readily available in local pharmacies.

158 The swallowing aid “Gloup original”, with a strawberry/banana flavor, was also tested  
159 (Rushwood B.V., Raamsdonksveer, NL). This product is composed of: water, carrageenan,

160 maltodextrin, potassium sorbate, sucrose, calcium chloride, citric acid, colour, and aroma.  
161 “Gloup original” is proposed as a swallowing gel for medicines, and contains carrageenans.  
162 The gel was directly poured from the 150 mL container at room temperature.

163 Two model fluids, with limited rheological complexity compared to the previous food systems,  
164 were also considered in this study. First, aqueous suspensions (1 and 3 % w/w in mineral  
165 water) of polyethylene oxide (PEO, CAS 25322-68-3, average molecular weight  $M_w = 10^6$   
166 g/mol) were used to further investigate the effect of elasticity. The polymer was left hydrating  
167 overnight in sealed containers under magnetic stirring. Finally, solutions of glycerol (Sigma-  
168 Aldrich, CAS Number 56-81-5) were used. Glycerol was diluted with mineral water to obtain  
169 an IDDSI level 1 mixture (72.8 % glycerol w/w), and an IDDSI level 3 mixture (98.8 % glycerol  
170 w/w).

171 Several shapes and sizes of SODF may be available for the same medication and dosage.  
172 Tablets and capsules sizes may range from 3 to 25 mm in length according to Jacobsen et al.  
173 (Jacobsen et al., 2016), but people tend to be more comfortable with round, white, medium-  
174 sized (between 8 and 12 mm in diameter) coated tablets (Fields et al., 2015; Overgaard et al.,  
175 2001; Radhakrishnan, 2016). Therefore, a large uncoated dark tablet and a HPMC capsule  
176 equivalent in size were selected (Table 1). Food supplements of *Spirulina platensis* available  
177 in these two formats were sourced from Anastore (“Spiruline Biologique”, 500 mg,  
178 [https://www.anastore.com/fr/articles/NA40\\_spiruline\\_bio.php](https://www.anastore.com/fr/articles/NA40_spiruline_bio.php)) and Vegavero (“Spirulina Bio”,  
179 1000 mg, <https://shop.vegavero.com/uk/p/Spirulina-Organic>).

## 180 *Methods*

### 181 IDDSI flow test

182 The IDDSI flow test was run at room temperature in triplicate to evaluate the IDDSI level of  
183 each liquid carrier (IDDSI, 2019). In this test, a standard luer slip tip syringe is filled up to the  
184 10 mL mark with the sample, and the liquid is then allowed to flow for 10 s. Based on the  
185 remaining volume left in the syringe, liquid samples are categorized in four levels of increasing

186 thickness: Level 0 (less than 1 mL remaining), Level 1 (1-4 mL remaining), Level 2 (4-8 mL  
187 remaining), Level 3 (no less than 8 mL remaining). If the liquid does not flow through the tip of  
188 the syringe, it is classified as Level 4. IDDSI Level 4 liquids can also be evaluated with the  
189 IDDSI spoon tilt test: they must hold their shape on a spoon and fall off easily if the spoon is  
190 tilted.

#### 191 Steady shear tests

192 The shear viscosity was assessed with a Modular Compact Rheometer (MCR) 102 (Anton  
193 Paar GmbH, Graz, Austria), at 25°C. A cone and plate geometry (diameter = 50 mm, cone  
194 angle = 4°, truncation = 500 µm), and a 0.5 mm gap were used to obtain flow curves in a range  
195 of shear rates between 0.5 and 800 reciprocal seconds. Three repetitions were performed for  
196 each sample.

#### 197 Extensional properties

198 The extensional properties of the samples were measured by capillary break-up rheometry  
199 using a HAAKE CaBER 1 (Thermo Electron, Karlsruhe, Germany) at room temperature. The  
200 initial separation between the two circular plates (6 mm in diameter) was set at 3 mm, and an  
201 axial displacement up to 10 mm was imposed in 50 ms to drive the filament thinning. The  
202 evolution in time of the midpoint diameter of the thread was measured with a laser micrometer  
203 with a beam thickness of 1 mm and a resolution of 20 µm. The extensional relaxation time was  
204 calculated with the CaBER Analysis software (Haake RheoWin Software, version 5.0.12) by  
205 fitting the data with the elastic (exponential) model. Five repetitions were performed for each  
206 sample. High-speed videos of the experiments were also taken at 1000 frames per second to  
207 record the shape evolution of the capillary thread using a Phantom V1612 high-speed camera  
208 (Vision Research, Wayne, NJ).

#### 209 *In vitro* swallowing

210 The effect of the rheological properties of the different liquid carriers on the dynamics of SODF  
211 swallowing was investigated *in vitro* with an experimental setup (Fig. 1) that considers the  
212 peristaltic motion induced by the tongue during the oral phase of swallowing. A comprehensive

213 description of this experimental setup, the discussion of the limitations and the validation  
214 against ultrasonic *in vivo* measurements has already been presented by Mowlavi et al., 2016.  
215 This setup has been used to test pharmaceutical formulations in Marconati et al., 2019b. A  
216 comparison with alternative *in vitro* approaches was presented in Marconati et al., 2019a.

217 The capsule or tablet was first positioned in the dry plastic membrane (25 mm wide), and  
218 aligned with its longitudinal axis. Thus, the smallest cross-section of the SODF was in the  
219 direction of the flow. Then, 4.5 mL of liquid carrier was carefully pushed in and after 2 min the  
220 roller movement was triggered. This contact time between SODF and liquid was controlled in  
221 order to limit the dissolution of the capsule/tablet before swallowing. The role of the salivary  
222 lubrication was not considered in this study.

223 The instantaneous position of the liquid carrier and the SODF during the *in vitro* swallowing  
224 experiment was recorded using a high-speed camera (model ac1920-155 mm, Basler,  
225 Ahrensburg, Germany) at 200 frames per second. In the following, the term “bolus” refers to a  
226 combination of liquid carrier and SODF swallowed together. The mass of residues left inside  
227 the plastic membrane after a swallow was also recorded for each experiment. At least three  
228 repetitions were performed for each set of experimental variables.

229 The time at which the front of the bolus (FO) exits the plastic membrane, and the time at which  
230 the tail of the bolus (TO) leaves the membrane were identified on the video recordings of each  
231 experiment. In this experimental setup, the plastic membrane plays the role of the oral cavity,  
232 therefore FO and TO are considered as characteristic oral transit times.

233 Image processing tools (ImageJ and GNU Octave) were used to extract the instantaneous  
234 position of the roller (corresponding to the bolus tail), and the SODF center of mass during the  
235 swallowing experiment up to TO.

236 The bolus length (BL) was measured between the roller and the bolus front at  $t_0$ , FO and TO.  
237 Similarly, the position of the SODF in the bolus was quantified by measuring the distance  
238 between the SODF front and the bolus front at  $t_0$ , FO and FO ( $\Delta$  front).

239 The aspect ratio of the bolus was evaluated at t0 and TO, as the ratio of the bolus length from  
240 bolus tail to bolus head to its maximum width (length/width).

241 Additionally, the difference in the angular position of the center of mass of the SODF and the  
242 angular position of the roller was followed up to FO:

$$243 \quad \Delta\theta = \theta_{\text{SODF}} - \theta_{\text{roller}} \quad (1)$$

244 A decreasing  $\Delta\theta$  indicates that the SODF was slower than the liquid carrier and moved towards  
245 the tail of the bolus, and inversely an increasing  $\Delta\theta$  shows that the SODF was flowing faster  
246 than the liquid and was moving toward the front of the bolus.

### 247 Statistical analysis

248 The results are shown in terms of the mean  $\pm$  the standard deviation. The statistical  
249 significance of the results was tested using one-way analysis of variance (ANOVA) and  
250 differences between group means were analyzed by Tukey's multiple comparison test with a  
251 probability level of 0.05 ( $p < 0.05$ ). Statistical analysis was carried out with Origin (version  
252 2020b, OriginLab Corporation, Northampton, MA).

## 253 **Results and discussion**

### 254 IDDSI flow test

255 The set of liquid carriers considered in this study was designed to obtain two different  
256 categories of consistencies: water and thin liquids on one side, and thicker liquids adapted for  
257 individuals with dysphagia on the other side. The consistency of each liquid carrier was first  
258 qualitatively evaluated according to the IDDSI framework (Table 2).

259 Apart from water, three groups of samples were obtained. The oat extract 0.3 % (w/w), and  
260 the suspensions of TUC 0.6 % (w/v), PEO 1 % (w/w), and glycerol 72.8 % (w/w) were classified  
261 as IDDSI Level 1. The oat extract 1 % (w/w), and the suspensions of TUC 2.4 % (w/v), PEO 3  
262 % (w/w), and glycerol 98.8 % (w/w) were classified as IDDSI Level 3. Group Original and TUC  
263 3.6 (w/v) were classified as IDDSI Level 4.

264 Gloup Original is marketed as an IDDSI Level 3 product, but it was classified here as IDDSI  
265 Level 4 since no outflow was measured in the 10 s test-time. This classification was confirmed  
266 with the IDDSI spoon tilt test. (Malouh et al., 2020) also classified this product as Level 4 when  
267 directly poured from the bottle.

### 268 *Rheological properties*

269 Flow curves obtained in steady shear are presented in Figure 2. Overall, the samples showed  
270 a shear thinning behavior, except for the mineral water and the glycerol solutions which are  
271 Newtonian fluids (Fig. 2). However, specific differences were observed.

272 TUC suspensions had a pronounced shear thinning behavior across this range of shear rates,  
273 independently of the concentration used, while PEO suspensions were less shear thinning,  
274 suggesting a viscosity plateau at low shear rates. The extent of this viscosity plateau  
275 decreased when increasing the polymer concentration (up to  $100 \text{ s}^{-1}$  for PEO L1, and up to  $1$   
276  $\text{s}^{-1}$  for PEO L3). Compared to TUC and PEO, the oat extracts had an intermediate shear  
277 thinning behavior. Similar results were reported by Marconati & Ramaioli (2020).

278 The flow curve of Gloup showed a strong shear thinning behavior too, as it can be expected  
279 for a product composed of carrageenan. Across the range of shear rates considered, Gloup,  
280 TUC L3, and TUC L4 had similar viscosities.

281 The four IDDSI Level 1 carriers had comparable shear viscosities at  $\dot{\gamma} = 50 \text{ s}^{-1}$ . TUC L1 had  
282 the lowest ( $30.76 \pm 3.12 \text{ mPa}\cdot\text{s}$ ), and the oat extract L1 had the highest ( $40.09 \pm 13.01 \text{ mPa}\cdot\text{s}$ ).  
283 To provide the reader with a benchmark, commercial orange juices have similar viscosities  
284 (Marconati et al., 2018). In contrast, shear viscosities at  $\dot{\gamma} = 50 \text{ s}^{-1}$  differed significantly between  
285 IDDSI Level 3 liquid carriers. Two groups were observed: oat extract L3 and TUC L3 were  
286 lower in viscosity than PEO L3 and glycerol L3 (approx. 275 and 670  $\text{mPa}\cdot\text{s}$ , respectively).

287 The shear rheology of texture modifiers is commonly reported at shear rates of 50 reciprocal  
288 seconds, which facilitates comparison between studies. However, it has been established that

289 shear rates for the whole swallowing process can vary from  $1 \text{ s}^{-1}$  in the mouth and the  
290 esophagus to  $1000 \text{ s}^{-1}$  in the pharynx (Gallegos et al., 2012; Nishinari et al., 2016).

291 According to Figure 2, liquid carriers with the same IDDSI level had different viscosities at low  
292 and high shear rates (i.e.,  $\leq 10 \text{ s}^{-1}$  and  $\geq 100 \text{ s}^{-1}$ , respectively), except for TUC suspensions  
293 and Gloup which are both similar, strongly shear thinning products. These results suggest that  
294 IDDSI levels represent different viscosity ranges if the fluids considered are Newtonian, slightly  
295 shear thinning or strongly shear thinning.

### 296 *Extensional properties*

297 The extensional properties of the liquid carriers were studied by Capillary Breakage  
298 Extensional Rheometry (CaBER). Selected images extracted from video recordings of the  
299 transient filament thinning until break-up for each sample are presented in Figure 3, and the  
300 temporal evolution of the midpoint filament diameter, normalized by the initial midpoint  
301 diameter is illustrated in Figure 4. Breakup time was extremely short (i.e.,  $< 0.05 \text{ s}$ ) for TUC L1  
302 and glycerol L1, and therefore no images are shown for these samples.

303 Different regimes of capillary thinning and break-up were observed, independently of the IDDSI  
304 level of the carrier. For TUC suspensions, Gloup, and glycerol solutions, the filament had a  
305 hour-glass shape (Fig. 3 d, f, g, h). The filament was rapidly evolving in time and short break-  
306 up time were measured (i.e.,  $\leq 0.5 \text{ s}$ ). For glycerol samples, the filament diameter decreased  
307 linearly in time, which is typically observed for Newtonian fluids (Anna & McKinley, 2000). For  
308 TUC and Gloup, an acceleration of filament break-up in a viscous dominated regime was  
309 observed, characteristic of shear thinning liquids (McKinley, 2005) (Fig. 4a).

310 In contrast, the liquid bridge formed by PEO suspensions and the oat extracts was cylindrical  
311 (Fig. 3 a, b, c, e). In this case, the radius of the cylindrical capillary decreased exponentially in  
312 time and larger break-up time were registered (Fig. 4b). This behavior is distinctive of elastic  
313 fluids (Anna & McKinley, 2000). Such elastic dominated regimes can be described by a single  
314 extensional relaxation time ( $\lambda_c$ ) (Arnolds et al., 2010). In the experimental conditions of this

315 study, the oat extracts had larger  $\lambda_c$  than the PEO suspensions (0.04 to 0.10, and 0.01 to 0.07,  
316 respectively). Similar results were obtained by Marconati & Ramaioli (2020).

317 Overall, larger break-up times were measured for IDDSI level 3 carriers compared to IDDSI  
318 level 1 samples. At higher thickener concentrations, the contribution of the viscous drainage  
319 on the filament thinning dynamics increased. This was also observed for the elastic liquid  
320 carriers, but in this case,  $\lambda_c$  also increased when increasing the polymers concentrations (Fig.  
321 5). Interestingly, for the oat extracts  $\lambda_c$  values increased rapidly with concentration while the  
322 increase in shear viscosity was moderate (Fig. 5). These samples may therefore be considered  
323 as elastic thin fluids.

### 324 *SODF in vitro swallowing*

325 The *in vitro* experiments aimed at understanding the effect of liquid carriers with different  
326 rheological properties on the swallowing dynamics of capsules and tablets. Bolus velocity,  
327 post-swallow residues, bolus elongation, and position of the SODF in the liquid carrier were  
328 first investigated with water, considered as a reference.

329 Snapshots from the experimental video recordings are presented in Figure 6. These pictures  
330 were taken at the beginning of the experiment ( $t_0$ ), when the front of the bolus reached the  
331 end of the simulated oral cavity (FO), and when the tail of the bolus exited the simulated oral  
332 cavity (TO).

### 333 Oral transit times

334 Characteristic oral transit times for the different carriers with or without SODF are presented in  
335 Figure 7.

336 With water, FO was not modified by the presence of SODF in the bolus, but TO was slightly  
337 delayed, meaning that capsules and tablets both slowed down bolus ejection (delay of 0.03  
338 and 0.06 s, respectively). These results suggest that large SODF only slightly influence bolus  
339 velocity when swallowed with water.

340 All tests performed with L1 liquids with and without SODF led to similar TO to water (without  
341 SODFF). When compared to water L1 liquids were therefore all able to avoid the slowing down  
342 induced by the presence of a capsule.

343 The oat extract L3, Gloup, and TUC L4, only slightly delayed FO and TO compared to water,  
344 while TUC L3 showed a transit time similar to water. Glycerol L3 showed significantly higher  
345 FO and TO. The oral transit time of the tablet with glycerol L3 was the longest of all the samples  
346 tested and reached 0.79 s, which is almost twice the transit time with water. This delay is  
347 attributed to the relatively high viscosity of this Newtonian sample at high shear rates (approx.  
348 650 mPa.s at  $\dot{\gamma} \geq 50 \text{ s}^{-1}$ ).

349 When swallowed with any IDDSI level 3 or 4 liquid carrier, both SODF delayed TO by 0.05 to  
350 0.2 s, following this increasing order in delay: TUC and Gloup < oat extract < PEO < glycerol  
351 (Fig. 7). This seems to be related to the shear viscosity of the carriers at  $\dot{\gamma} = 300 \text{ s}^{-1}$ . No  
352 differences were observed between capsules and tablets.

353 This suggest that the impact of the SODF on the oral transit time also depends on the  
354 rheological properties of the liquid carriers at high shear rates. In other words, delays increase  
355 with increasing high shear rates viscosities. This can be explained by the small gaps present  
356 around the SODF during the flow, where high shear rates can be reached.

357 These results are consistent with a previous study (Marconati et al., 2018) in which longer  
358 transit times, higher variability and lower bolus velocities were registered for large SODF  
359 (prolate spheroids, equivalent in volume to a  $d = 10 \text{ mm}$  sphere) in glycerol and orange juice  
360 (viscosity =  $1.05 \pm 0.05 \text{ Pa.s}$  and  $0.03 \pm 0.01 \text{ Pa.s}$ , respectively).

### 361 Post-swallow residues

362 The mass of residues left in the plastic membrane was measured after each swallow. With  
363 water, post-swallow residues were increased by the presence of the tablet in the bolus. This  
364 was probably related to the fast dissolution of the uncoated tablet in water since traces of dark  
365 residues were observed in the membranes.

366 Overall, the amount of post-swallow residues increased with the shear viscosity of the samples  
367 and no clear effect of the SODF on post-swallow residues was observed (Fig. 8). Among the  
368 IDDSI level 1 carriers, the glycerol solution left more residues (approx. 0.8 mL) than the other  
369 liquid carriers (between 0.5 and 0.6 mL). For oat extracts and TUC, no significant effect of the  
370 concentration was observed. In contrast, the post-swallow residues were significantly higher  
371 for PEO and glycerol L3 compared to the lower concentration solutions classified as IDDSI L1,  
372 and reached approx. 0.9 and 1 mL which is twice the volume of residues measured with water.  
373 Gloop left also an important amount of post-swallow residues in the membrane (0.9 to 1 mL,  
374 equivalent to glycerol L3).

375 Excessive oropharyngeal residues can cause discomfort (i.e., unpleasant feeling that the food  
376 sticks in the throat), and multiple swallows can be necessary to clear the residues, which may  
377 decrease the palatability of a product. Residues can also lead to aspiration by people suffering  
378 from swallowing disorders and result in respiratory complications, such as pneumonia.  
379 Therefore, when developing swallowing aids, care must be taken to avoid the adverse effects  
380 of increased viscosity on residues and palatability. Xanthan gum-based thickeners, like TUC,  
381 are often preferred to starch-based thickeners in the management of dysphagia because they  
382 improve the swallowing safety without increasing the oropharyngeal residues (Hadde et al.,  
383 2019; Ortega et al., 2020; Rofes et al., 2014). Just as TUC, the oat extracts evaluated in this  
384 study resulted in limited *in vitro* post-swallow residues. Only clinical results can however  
385 confirm a positive impact for people with dysphagia.

### 386 Bolus elongation

387 The length of the bolus was evaluated by image analysis at t<sub>0</sub>, t<sub>FO</sub>, and t<sub>TO</sub>, for each set of  
388 liquid carrier and SODF. At t<sub>0</sub>, BL was 43.1 ± 0.8 mm without SODF, 47.0 ± 1.2 mm with  
389 capsules, and 47.2 ± 1.4 mm with tablets. The presence of capsules and tablets in the bolus  
390 increased its volume, resulting in a longer initial bolus and in a higher risk of pre-swallow  
391 leakages, especially with water and IDDSI level 1 fluids.

392 At t FO, for SODF swallowed with water or TUC L1, an increase in BL was observed. This is  
393 attributed to liquid leakages before the experiment was triggered. In contrast, a decrease in BL  
394 was noticed for the most viscous samples (e.g. PEO and glycerol L3), which may be related  
395 to the partial loss of carrier during swallowing (i.e., left as residue in the membrane).

396 In this *in vitro* experiment, the liquid ejected from the plastic membrane is subject to  
397 gravitational acceleration, which induces elongation, and to die swell in the case of viscoelastic  
398 liquids (i.e., expansion). The shear viscosity of the liquid carrier and the interaction between  
399 both phenomena will determine the bolus shape at TO.

400 Water swallows resulted in long boluses at TO (Fig. 6a and Fig. 9). BL was almost doubled  
401 between t0 and TO, and the presence of SODF increased bolus elongation even further. This  
402 is not desirable for patients with dysphagia because stretched boluses are more likely to break  
403 during swallowing and may increase the risk of aspiration *in vivo* (Hadde et al., 2019).

404 Results similar to water were observed with TUC L1 (bolus elongation > 1.75, increased by  
405 the presence of SODF). Shorter boluses were measured for the other IDDSI level 1 liquid  
406 carriers (oat extract, PEO, and glycerol), with no significant differences in BL when swallowing  
407 the SODF (Fig. 9).

408 All IDDSI level 3 fluids had shorter boluses at TO, compared to water (Fig. 6 and 9), and no  
409 significant effect of the SODF was observed. PEO L3 samples resulted in the lowest bolus  
410 elongation values (0.80 to 0.85) and TUC L3 samples in the highest bolus elongation values  
411 (1.20 to 1.40). Bolus elongation was also limited for Gloup and TUC L4, and was about 1.05  
412 for both carriers (Fig. 6 and 9).

413 These results suggest that bolus shape at the exit of the oral cavity is related to the viscosity  
414 of the liquid carriers at high shear rates (BL of L3 fluids < BL of L1 fluids), and to the extensional  
415 properties of the liquid carriers (BL of oat extract L1 similar to BL of TUC L3).

416 A compact bolus shape has been suggested as a way to promote a smoother and more  
417 controlled bolus flow through the pharynx based on videofluoroscopy observations (Hadde et

418 al. 2019). However, this parameter should be further investigated *in vivo*, to evaluate the impact  
419 of a broader range of extensional and viscoelastic properties on bolus fragmentation.

#### 420 Bolus aspect ratio

421 The aspect ratio of the bolus was the same for all the liquid carriers at  $t_0$  (aspect ratio =  $4.7 \pm$   
422  $0.3$ ). But, at  $T_0$ , the aspect ratio of the bolus depended on the rheological properties of the  
423 samples as discussed in the previous section. Bolus aspect ratio at  $T_0$  varied between  $13.1 \pm$   
424  $1.4$  for water and  $3.2 \pm 0.2$  for PEO L3 (Appendix 3).

425 Hadde et al., (2019) measured the bolus aspect ratio in the pharynx (at the upper esophageal  
426 sphincter opening) during a videofluoroscopy swallow study (VFSS) with healthy patients.  
427 Authors reported bolus aspect ratios of 6.8, 5.8, and 5.6 for TUC samples mixed with barium  
428 sulphate with an IDDSI level 1, 3, and 4 respectively. Our results *in vitro* are similar for TUC  
429 L3 and L4, but we observed a larger aspect ratio for TUC L1. However, it must be noted that  
430 the viscosity at  $\dot{\gamma} = 50 \text{ s}^{-1}$  of our TUC L1 sample was lower than the one used by Hadde et al.,  
431 (2019), as well as the volume of liquid swallowed.

#### 432 Position of the SODF

433 As can be seen in Figure 6, the position in the bolus of capsules and tablets varied according  
434 to the liquid carrier used. In order to examine this phenomenon in more detail, the relative  
435 position of the SODF with respect to bolus front was quantified from the videos of the  
436 experiments at  $t_0$ ,  $F_0$ , and  $T_0$  (Fig. 10).

437 Before the swallow, the position of the SODF depended on its buoyancy in the liquid carrier.  
438 In water, the low density ( $0.7 \text{ g/mL}$ ) of the capsules led to floating, and to positioning close to  
439 the front of the bolus (Fig. 6 and 10). In contrast, the tablet (density of  $1.2 \text{ g/mL}$ ) settled out  
440 and positioned close to the tail of the bolus (Fig. 6 and 10). Similar results were observed with  
441 the IDDSI Level 1 carriers. But with IDDSI L3 fluids, tablets were found in the middle of the  
442 bolus, except with the oat extract.

443 All the liquid carriers used in this study had a density of approx. 1.0 g/mL, except the glycerol  
444 solutions, which had a density of 1.2 g/mL. So, glycerol solutions and tablets had the same  
445 density; the tablets did not sediment and had the same position than capsules at t0 in glycerol  
446 boluses.

447 When swallowed with water, both SODF lagged toward the bolus tail during *in vitro* swallowing  
448 (Fig. 6 and 10). Under the imposed squeezing action of the roller, water was able to flow  
449 through the gap present around the SODF, leading to the solid lagging behind (Marconati et  
450 al., 2018). Capsules and tablets entered the simulated pharynx after the bulk of the liquid, with  
451 no liquid left to help transport them out. This phenomenon has already been reported by  
452 Marconati et al., (2018) in a similar *in vitro* experiment with model large spherical tablets in  
453 orange juice.

454 These results suggest that water is not an efficient carrier for capsules and tablets. It flows  
455 faster than the SODF, which lags behind. Multiple swallows or larger volumes of water may  
456 then probably be needed to transport the SODF from the oral cavity to the esophagus, which  
457 multiply the risks for patients with dysphagia (Hey et al., 1982; Stegemann et al., 2012;  
458 Yamamoto et al., 2014). Actually, *in vivo* studies have shown that when placebos could not be  
459 swallowed at the first attempt, they remained mainly in the mouth of the patients (Schiele et  
460 al., 2015; Yamamoto et al., 2014).

461 Comparable results were obtained with TUC L1. The liquid bolus was stretched and the SODF  
462 was close the bolus tail at t FO and at t TO (Fig. 6 and 10). But differences were observed with  
463 the other IDDSI level 1 liquid carriers. At t TO, in PEO and glycerol (L1), capsules were  
464 positioned in the middle of the liquid bolus, and in the oat extract both capsules and tablets  
465 were found at the front of the liquid bolus (Fig. 6 and 10). This is considered as an improvement  
466 in the transport of the SODF because it suggests that the solid may be efficiently embedded  
467 in the carrier during the whole swallowing process.

468 In thicker liquid carriers (IDDSI L3 and L4), capsules and tablets were either pushed in front of  
469 the bolus or transported in the middle (TUC L3 + capsule, and glycerol samples) (Fig. 6 and  
470 10). Therefore, all the liquid carriers tested improved the transport of the SODF considered in  
471 this study, except TUC L1, although this fluid led to low post swallow residues.

472 Indeed, the other criteria commented before (bolus shape, post-swallow residues, and oral  
473 transit times) should also be taken into account to decide which carrier to prefer (Table 3). The  
474 oat extract L1 appears as very good option to promote safe swallowing of SODF because it  
475 transported capsules and tablets at the front of a compact bolus, and only slightly increase oral  
476 transit times, without increasing too much the post-swallow residues. Clinical studies are,  
477 however, necessary to confirm these results in healthy and dysphagic patients.

#### 478 Capsules vs tablets.

479 In order to further explore the differences between the transport of capsules and tablets during  
480 *in vitro* swallowing, the position of the SODF was also followed during the whole experiment.  
481 Data are presented in Figure 11, separated by type of SODF and IDDSI levels.

482 Capsules seemed to adhere to the membrane mimicking the oral cavity during the first part of  
483 the experiment (i.e.,  $t < 0.15$  s) with all the liquid carriers, except glycerol solutions (Fig. 11).  
484 At the beginning of the test, the capsule did not move while the liquid was able to flow forward  
485 ( $\Delta\theta$  decreased). The capsule then reached the bolus tail ( $\Delta\theta$  approx.  $-15^\circ$ ), and under the  
486 squeezing action imposed by the roller it finally detached from the sidewall. Then, during the  
487 last part of the experiment, two different scenarios were observed for the capsules. With water  
488 and TUC (L1 & L3), the capsule was pushed forward together with the liquid bolus (constant  
489  $\Delta\theta$ ), while with the other carriers, the capsule moved faster than the liquid bolus (increasing  
490  $\Delta\theta$ ) (Fig. 11). When swallowed with glycerol (L1 & L3), no adhesion was observed between  
491 the capsules and the membrane,  $\Delta\theta$  decreased continuously (Fig. 11)

492 Tablets adhered significantly less to the membrane than the capsules at the beginning of the  
493 experiment (Fig. 11). With water, glycerol (L1 and L3), TUC L1, and Gloup,  $\Delta\theta$  decreased

494 continuously during the experiment (Fig. 11). With the other liquid carriers,  $\Delta\theta$  was first  
495 constant. Then, it increased around 0.1 s to reach the front of the bolus ( $\Delta\theta$  approx.  $+15^\circ$ ), or  
496 a plateau around  $\Delta\theta = 5^\circ$ , depending on the liquid carrier involved (Fig. 11). Overall, these  
497 results show that the tablets rapidly overcame the disadvantage of their initial position.

498 According to these results, the initial position of the SODF in the liquid bolus do not govern the  
499 subsequent evolution during swallowing. However, the adhesion of the SODF with the  
500 membrane had a significant impact on the swallowing dynamics of the solids and it should be  
501 further investigated.

502 Concerning the adhesion, one limitation of this study is that the contact time of the liquids and  
503 the SODF before triggering the *in vitro* swallowing was 2 min, which is longer than the typical  
504 *in vivo* contact time. Due to experimental constraints, it was not possible to reduce this  
505 immersion time. In these experimental conditions, the uncoated tablet adhered less to the  
506 plastic membrane than the HPMC capsule. Since in glycerol solutions, neither the capsule nor  
507 the tablet seemed to adhere to the membrane, the differences observed could be due to a  
508 partial dissolution of the SODF surfaces in aqueous suspensions or to a lower adhesion in  
509 presence of glycerol solutions. Furthermore, it should be noted that the plastic membrane  
510 simulating the oral cavity in this experimental setup may not have the same mechanical and  
511 interfacial properties as the buccal mucosa.

512 The adhesion of SODF to the mucus membranes from the oral cavity to the stomach has been  
513 investigated before, as it can be responsible of esophageal damage (Channer & Virjee, 1986;  
514 Chisaka et al., 2006; Hey et al., 1982; Perkins et al., 1994). However, contradicting results can  
515 be found in the literature about the adhesion of HPMC capsules to the mucosa. On one hand,  
516 using an *in vitro* setup incorporating a section of porcine esophageal mucosa moistened with  
517 saliva Smart et al., (2013) concluded that tablets coated with HPMC had significant adhesive  
518 properties. On the other hand, static and kinetic friction coefficients between HPMC coated  
519 tablets and an artificial skin were shown to reduce almost to 0 when the capsules were  
520 previously immersed in water (Shimasaki et al., 2019). Authors considered that the HPMC

521 coating acted as a lubricant between the formulation and the artificial skin, and concluded that  
522 this type of tablets would be easier to swallow than uncoated tablets when ingested with water.

## 523 **Conclusions**

524 This study used an *in vitro* artificial throat to study the dynamics of different sets of liquid  
525 carriers and SODF during the oral phase of swallowing. The effect of the rheological properties  
526 of the carriers on bolus velocity, bolus shape, post-swallow residues, and SODF position in the  
527 bolus were investigated. Experiments provided new insights on the transport of capsules and  
528 tablets in a peristaltic flow relevant to the oral phase of swallowing.

529 Low viscosity Newtonian fluids, like water, are not the most efficient carriers for SODF. When  
530 swallowed with water, capsules and tablets did not impact significantly the velocity of the bolus,  
531 but they lagged behind the liquid bolus, suggesting a higher risk of adhesion with the mucosa  
532 after the oral phase, because of the low kinetic energy of the liquid following the SODF.

533 The ability of the liquid to transport the SODF and their position in the bolus was improved by  
534 increasing the viscosity of the liquid carrier above 50 mPa.s at high shear rates ( $\dot{\gamma} = 300 \text{ s}^{-1}$ ).  
535 However, higher viscosities are associated with higher post-swallow residues, which could  
536 increase the risk of post-swallowing aspiration.

537 At equivalent shear viscosity (between 30 and 40 mPa.s,  $\dot{\gamma} = 50 \text{ s}^{-1}$ ), the position of the SODF  
538 in the bolus was positively affected by the elastic properties of the carriers (extensional  
539 relaxation time of at least 10 ms). Capsules and tablets were transported toward the front of  
540 the bolus, which is considered more advantageous from a flow perspective: maintaining a drag  
541 on the SODF during the oral phase could indeed prevent adhesion with the mucosa in the  
542 following phases of swallowing. Bolus elongation at the exit of the oral cavity was also  
543 positively related to the extensional properties of the carriers, suggesting that such liquids  
544 could promote a more controlled bolus flow through the pharynx, and reduce aspiration risks.

545 Thin elastic liquid formulations, like the oat extract evaluated in this study, therefore appear as  
546 an interesting option with a potential to promote safe swallowing of SODF. Clinical studies are  
547 however necessary to confirm if a positive effect is observed in dysphagic patients.

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## 550 **Ethical Statements**

551 Conflict of Interest: The authors declare that they do not have any conflict of interest.

552 Ethical Review: This study does not involve any human or animal testing.

## 553 **Data Availability Statement**

554 The data that support the findings of this study are available from the corresponding author  
555 upon reasonable request.

556 Supplementary data associated with this article can be found in Appendix.

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Capsule "Spiruline Biologique"	<i>Spirulina platensis</i> powder, HPMC capsule	Size 0	22 mm long 7.5 mm width	2.93	24.1 %	861 mm <sup>3</sup>	0.59 g	0.7
Tablet "Spirulina Bio"	<i>Spirulina platensis</i> compressed powder	Oblate, scored	22 mm long 7 mm width	3.14	26.7 %	842 mm <sup>3</sup>	1.02 g	1.2

756

757 Table 2: Classification of the liquid carriers used in this study according to the IDDSI testing

758 methods (flow test and spoon tilt test), at room temperature.

Carrier	IDDSI Flow test		Density (g/mL)	Abbreviated name
	Volume remaining (mL) in the syringe after 10 s	Interpretation (IDDSI classification)		
Mineral water	0	0	1.00 ± 0.00	Water
Oat extract 0.3 % (w/w)	2.75	1	0.98 ± 0.00	Oat extract L1
Oat extract 1 % (w/w)	9.00	3	0.98 ± 0.00	Oat extract L3
ThickenUp Clear 0.6 % (w/v)	1.25	1	1.00 ± 0.01	TUC L1
ThickenUp Clear 2.4 % (w/v)	9.50	3	1.00 ± 0.01	TUC L3
ThickenUp Clear 3.6 % (w/v)	10	4	1.02 ± 0.00	TUC L4
Gloup Original	10	4	1.05 ± 0.01	Gloup L4
PEO 1 % (w/w)	1.75	1	1.00 ± 0.01	PEO L1
PEO 3 % (w/w)	9.50	3	1.00 ± 0.01	PEO L3
Glycerol 72.8 % (w/w)	1.50	1	1.18 ± 0.00	Glycerol L1
Glycerol 98.8 % (w/w)	9.50	3	1.24 ± 0.01	Glycerol L3

759

760 Table 3: Relevant criteria to select a SODF carrier.

Carrier	SODF position in the bolus †	Amount of residues ‡	Bolus elongation §	Oral transit Time ¶
<b>Oat extract L1</b>	Front	Low	Moderate	Fast
<b>Oat extract L3</b>	Front	Moderate	No elongation	Moderate
<b>TUC L4</b>	Front	Moderate	No elongation	Moderate
<b>PEO L3</b>	Front	High	Shortening	Slow
<b>Gloup L4</b>	Front	High	No elongation	Moderate
<b>PEO L1</b>	Middle	Low	Moderate	Fast
<b>Glycerol L1</b>	Middle	Moderate	Moderate	Fast
<b>TUC L3</b>	Middle	Moderate	Moderate	Fast
<b>Glycerol L3</b>	Middle	High	No elongation	Slow
<b>Water</b>	Back	Low	High	Fast
<b>TUC L1</b>	Back	Low	High	Fast

761

762 † Front:  $\Delta$  front at TO < 10°; Back:  $\Delta$  front at TO > 50°;  
763 ‡ Low: between 0.4 and 0.6 mL; High: > 0.9 mL  
764 § Shortening: BL ratio at TO < 1; Moderate: BL ratio at TO between 1.1 and 1.6; High: BL ratio  
765 at TO > 1.6  
766 ¶ Fast: TO between 0.4 and 0.5 s; Slow: TO > 0.6 s

767

## 768 **Figure legends**

769 **Figure 1:** Schematics of the *in vitro* setup used to replicate the oral phase of swallowing,  
770 adapted from Marconati & Ramaioli (2020).

771 **Figure 2:** Steady shear viscosity of the different liquids used in this study as carriers.

772 **Figure 3:** Filament thinning of (a) Oat extract L1, (b) PEO L1, (c) Oat extract L3, (d) TUC L3,  
773 (e) PEO L3, (f) Glycerol L3, (g) Gloup L4, (h) TUC L4. Representative pictures of each liquid  
774 carrier at t 0, t  $\frac{1}{4}$  breakup, t  $\frac{1}{2}$  breakup, t  $\frac{3}{4}$  breakup, and t breakup (value of t breakup for this  
775 specific sample is indicated on the image).

776 **Figure 4:** Evolution of the filament midpoint diameter in time, up to t breakup, for TUC, glycerol,  
777 and Gloup samples (a). The curves are represented on a lin/lin scale for these non elastic  
778 samples. In (b) the curves for oat extracts, and PEO samples are represented using a (log/lin  
779 scale) to show the elastic behavior. Representative curves are presented.

780 **Figure 5:** Extensional relaxation time of the liquid carriers in relation to their shear viscosity at  
781  $\dot{\gamma} = 50 \text{ s}^{-1}$ .

782 **Figure 6:** Snapshots of representative *in vitro* swallows (capsules and tablets): (a) water, (b)  
783 oat extract L1, (c) TUC L1, (d) PEO L1, (e) glycerol L1, (f) oat extract L3, (g) TUC L3, (h) PEO  
784 L3, (i) glycerol L3, (j) Gloup L4, (k) TUC L4.

785 **Figure 7:** Characteristic oral transit time TO measured *in vitro* for the different liquid carriers  
786 alone (O, round label), or with a SODF (X, cross label), in relation to their shear viscosity at  
787  $\dot{\gamma} = 50 \text{ s}^{-1}$ . Empty circles indicate that the samples had a relaxation time  $\lambda_c \geq 10 \text{ ms}$ .

788 **Figure 8:** Calculated volumes of residues left in the plastic membrane simulating the oral cavity  
789 after *in vitro* swallowing for the different liquid carriers alone (O, round label), or with a SODF

790 (X, cross label), in relation to their shear viscosity at  $\dot{\gamma} = 50 \text{ s}^{-1}$ . Empty circles indicate that the  
791 samples had a relaxation time  $\lambda_c \geq 10 \text{ ms}$ .

792 **Figure 9:** Bolus elongation at TO (ratio of the bolus length at  $t_0$ ) for the different liquid carriers  
793 alone (O, round label), or with a SODF (X, cross label), in relation to their shear viscosity at  
794  $\dot{\gamma} = 300 \text{ s}^{-1}$ . Empty circles indicate that the samples had a relaxation time  $\lambda_c \geq 10 \text{ ms}$ .

795 **Figure 10:** Quantification by image analysis of the relative position of the capsule/tablet with  
796 respect to bolus front at TO.

797 **Figure 11:** Position of the SODF during *in vitro* swallowing with different liquid carriers:  
798 capsules in water and L1 fluids (a), in L3 and L4 fluids (b), and tablets in water and L1 fluids  
799 (c), in L3 and L4 fluids (d).

800

Figure 1

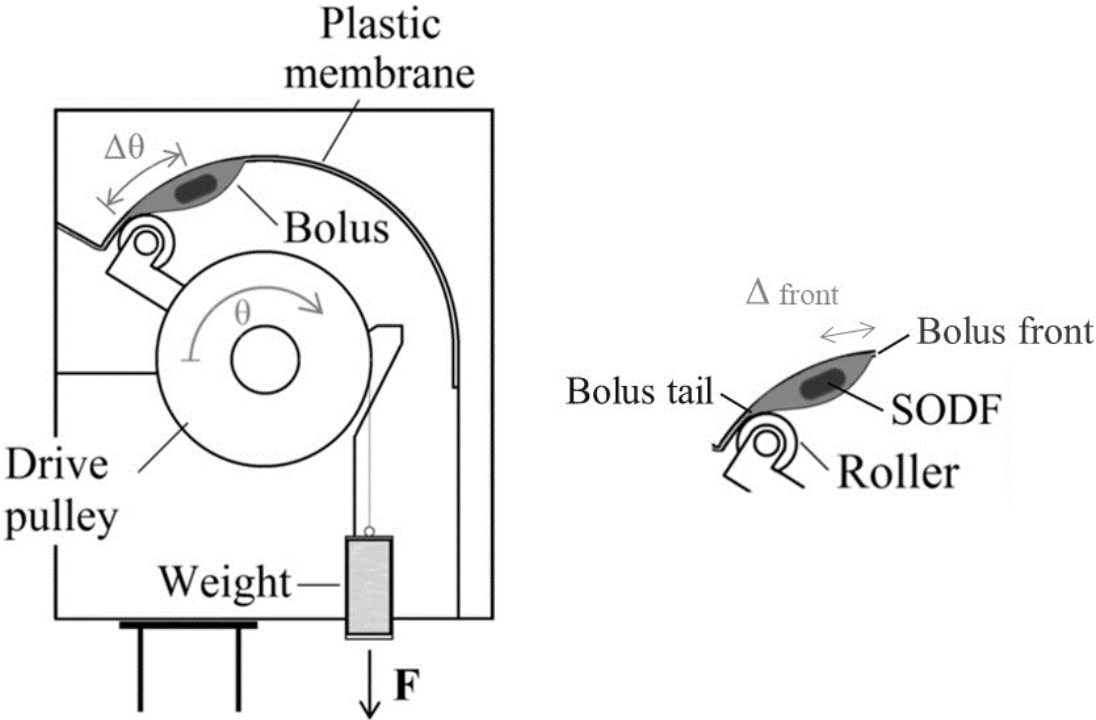


Figure 2

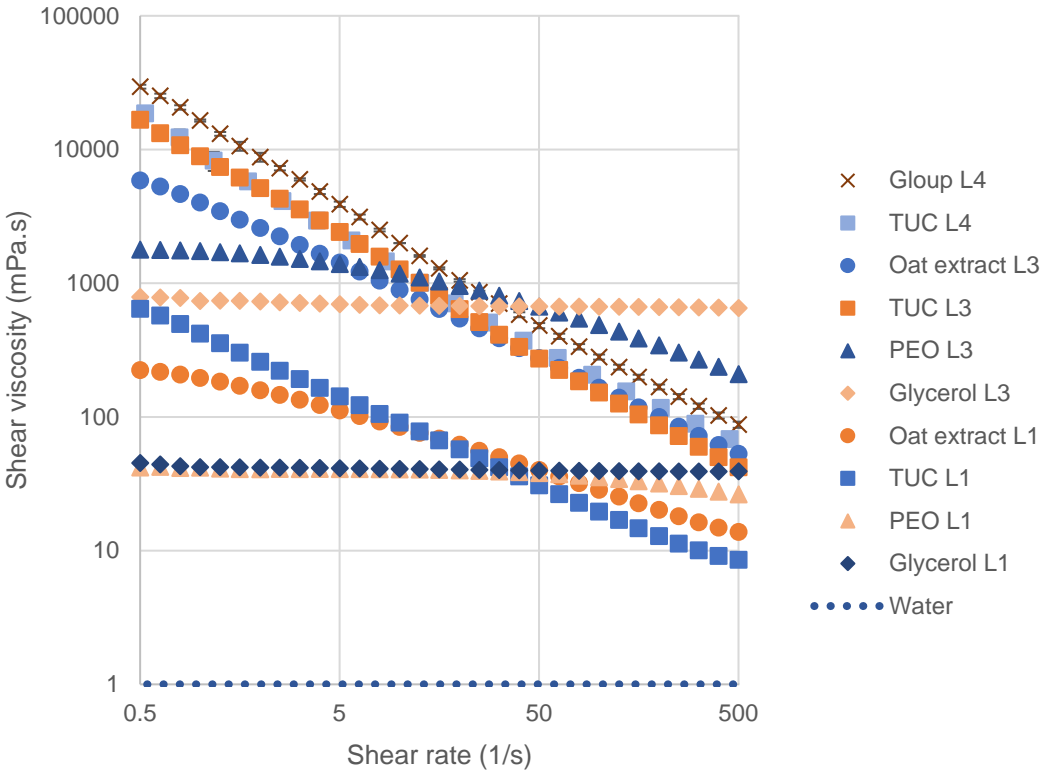


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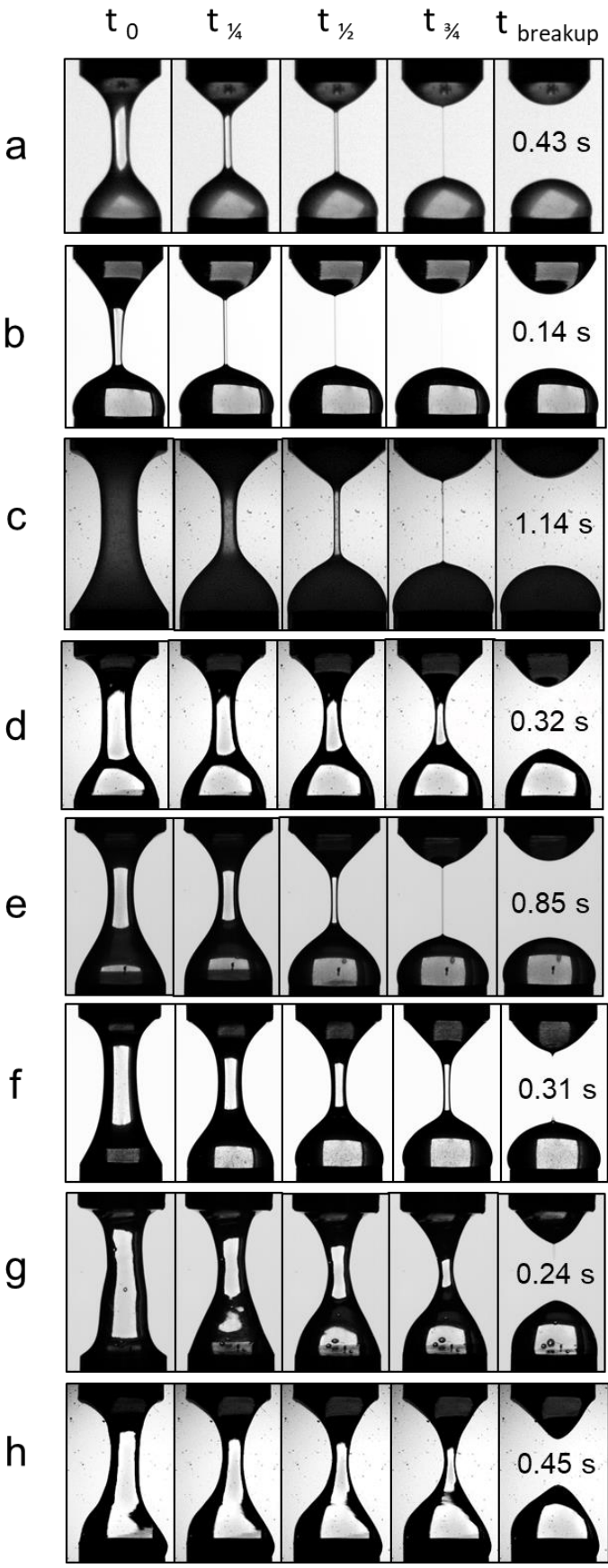


Figure 4 a

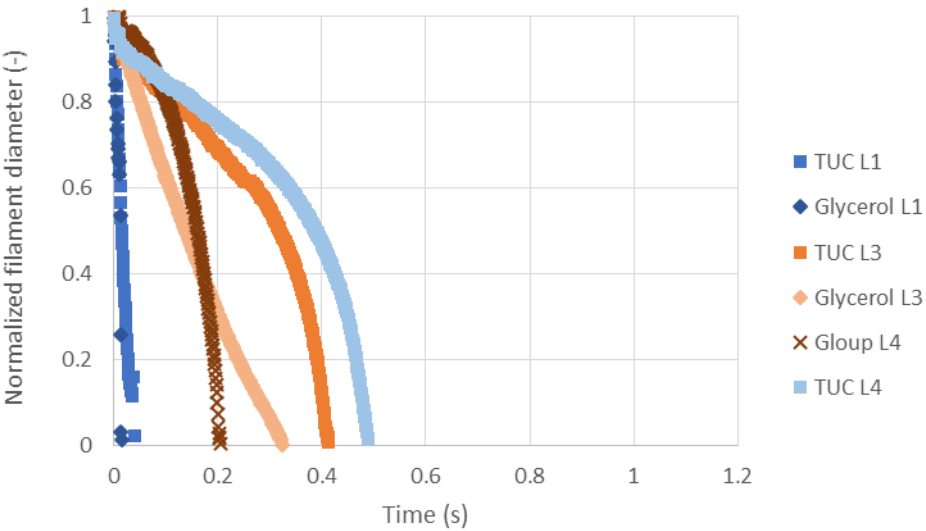


Figure 4 b

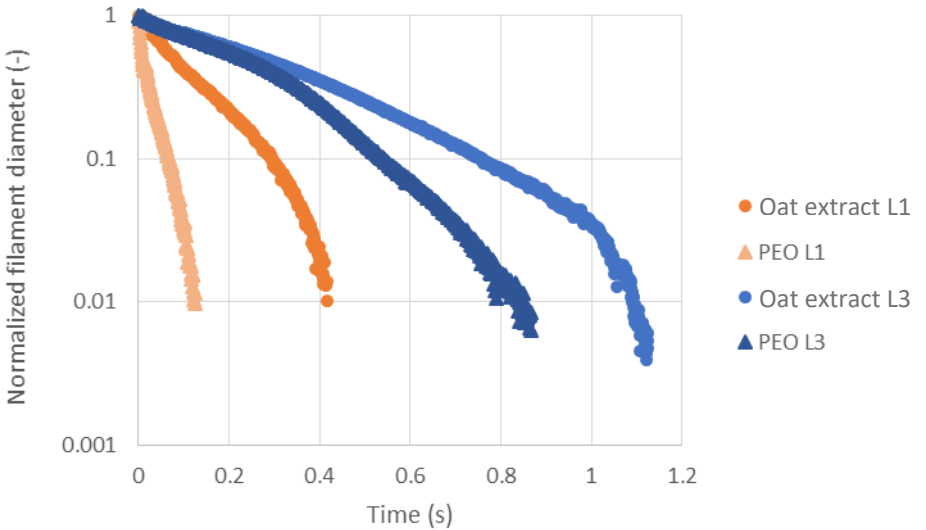


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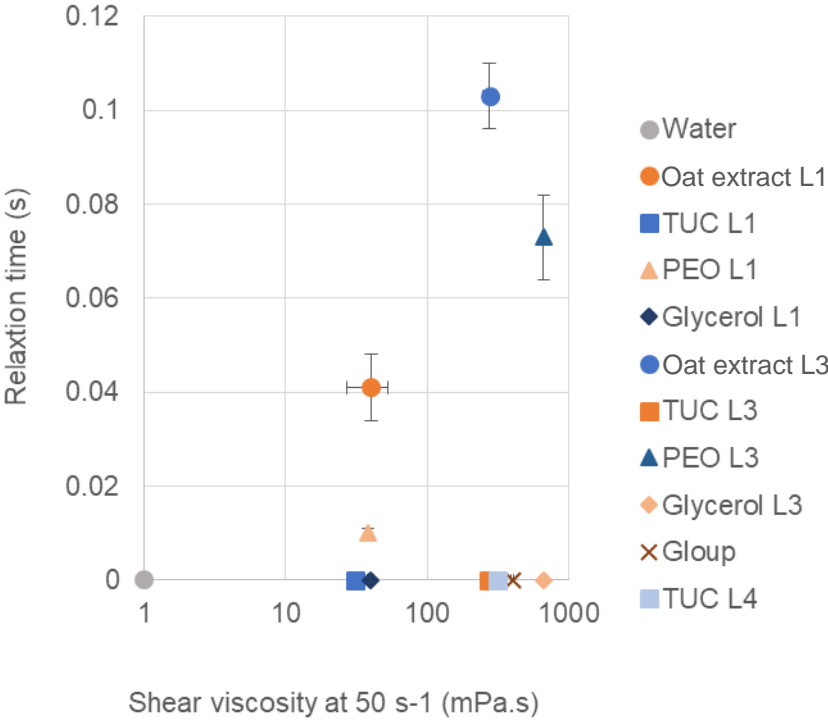


Figure 6

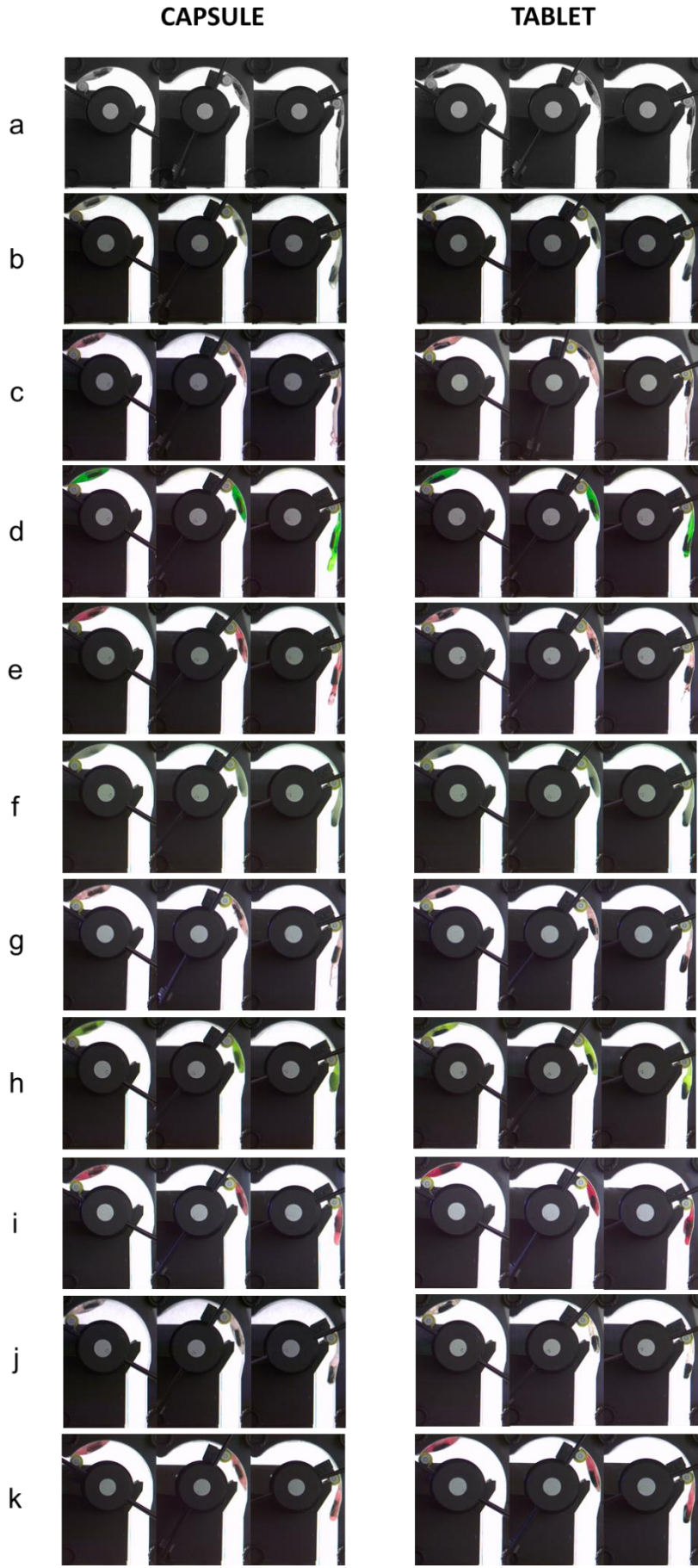


Figure 7

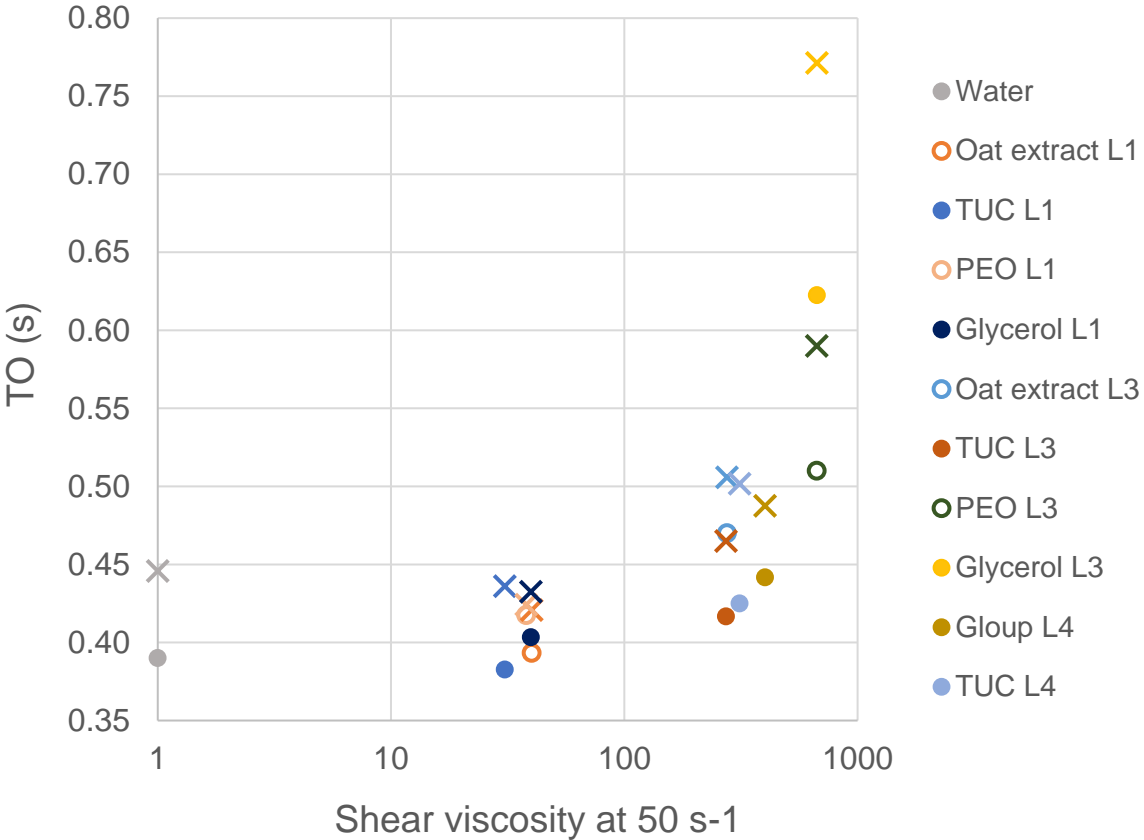


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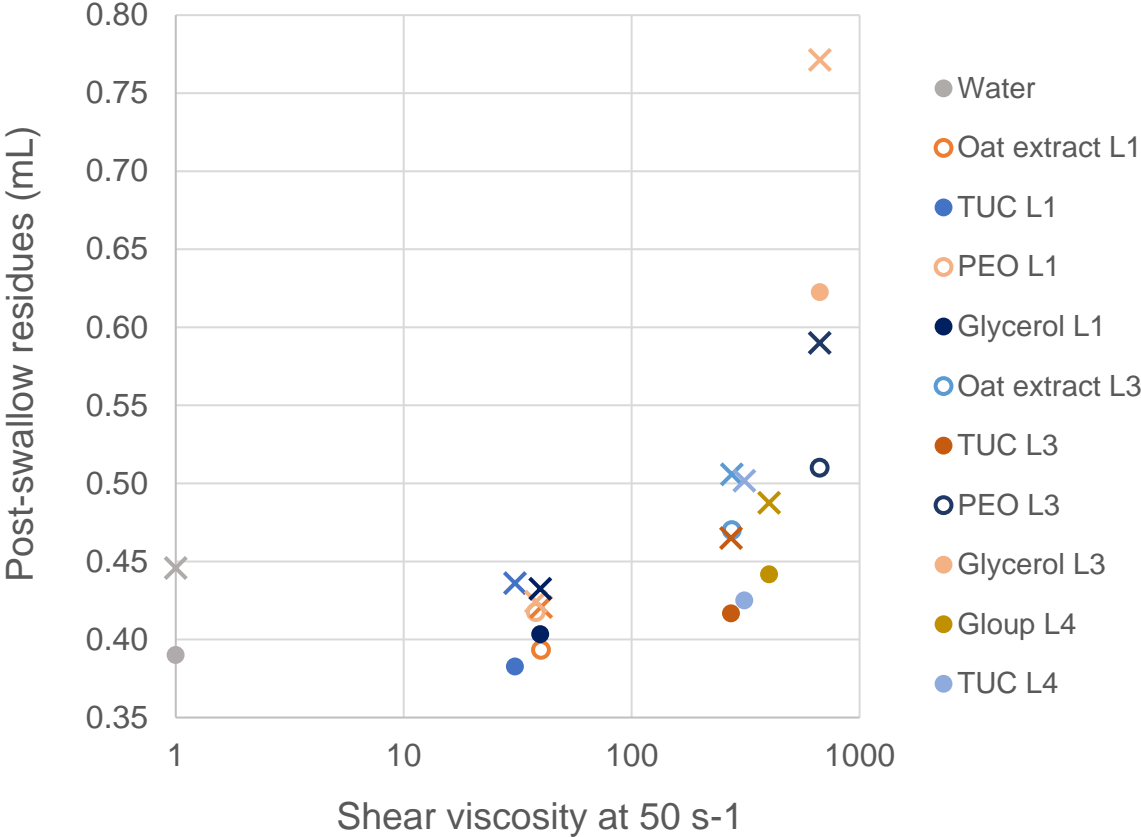


Figure 9

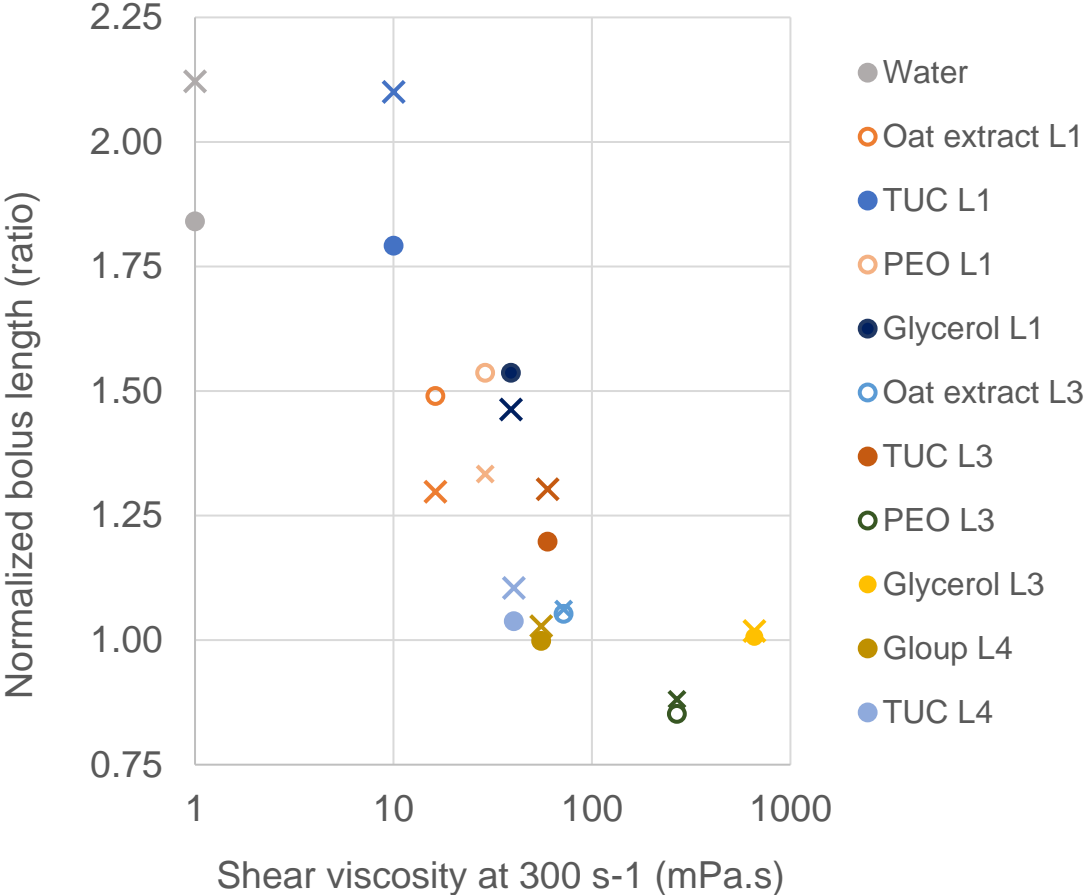


Figure 10

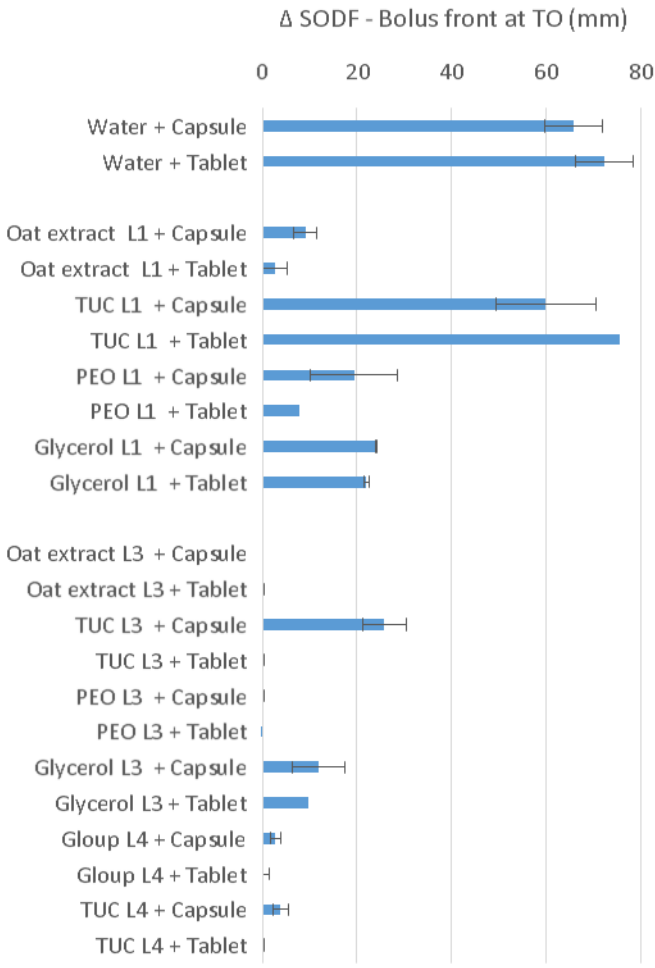


Figure 11 a

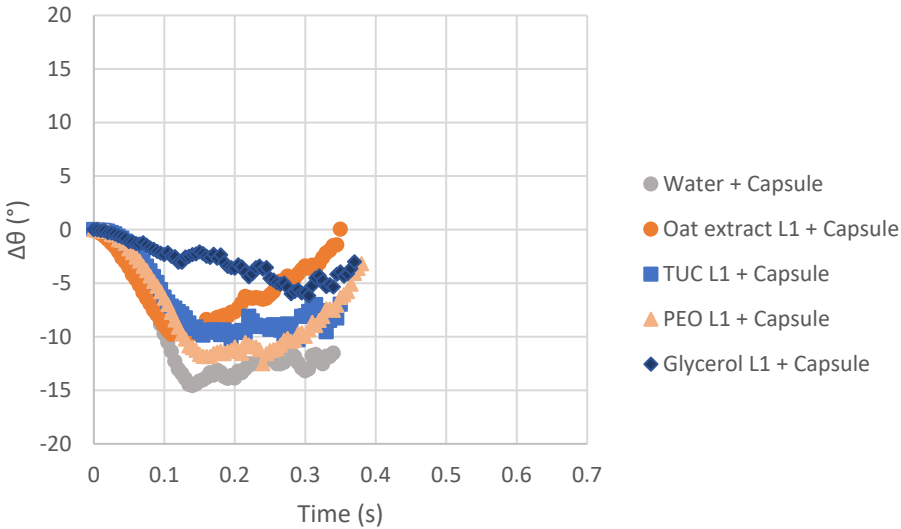


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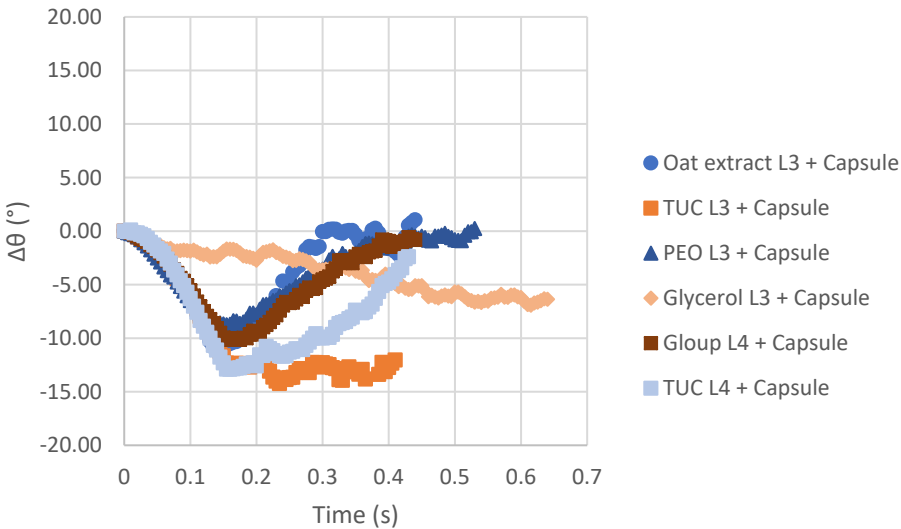


Figure 11 c

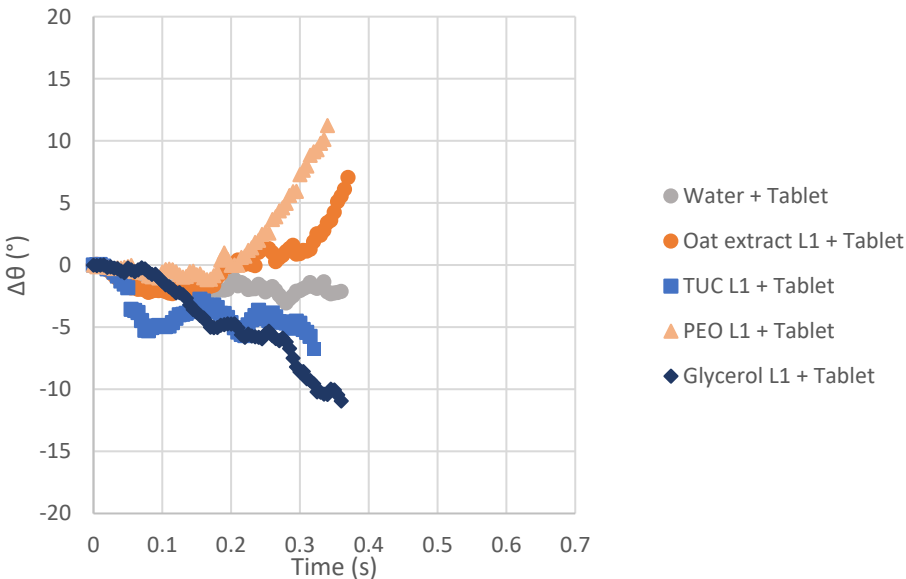


Figure 11 d

