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Abstract

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

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

Introduction

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Materials and methods

Materials

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

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

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

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

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

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

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

Methods

IDDSI flow test

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

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

Steady shear tests

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

Extensional properties

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

In vitro swallowing

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

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

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

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

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

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

The bolus length (BL) was measured between the roller and the bolus front at t0, FO and TO. Similarly, the position of the SODF in the bolus was quantified by measuring the distance between the SODF front and the bolus front at t0, FO and FO (Δ front).

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

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

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

A decreasing Δθ indicates that the SODF was slower than the liquid carrier and moved towards the tail of the bolus, and inversely an increasing Δθ shows that the SODF was flowing faster that the liquid and was moving toward the front of the bolus.

Statistical analysis

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

Results and discussion

IDDSI flow test

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

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

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

Rheological properties

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

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

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

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

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

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

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

Extensional properties

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

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

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

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

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

SODF in vitro swallowing

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

Snapshots from the experimental video recordings are presented in Figure 6. These pictures were taken at the beginning of the experiment (t0), when the front of the bolus reached the end of the simulated oral cavity (FO), and when the tail of the bolus exited the simulated oral cavity (TO).

Oral transit times

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

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

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

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

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

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

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

Post-swallow residues

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

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

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

Bolus elongation

The length of the bolus was evaluated by image analysis at t0, t FO, and t TO, for each set of liquid carrier and SODF. At t0, BL was 43.1 ± 0.8 mm without SODF, 47.0 ± 1.2 mm with capsules, and 47.2 ± 1.4 mm with tablets. The presence of capsules and tablets in the bolus increased its volume, resulting in a longer initial bolus and in a higher risk of pre-swallow leakages, especially with water and IDDSI level 1 fluids.

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

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

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

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

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

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

A compact bolus shape has been suggested as a way to promote a smoother and more 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 t0 (aspect ratio = 4.7 ±
422 0.3). But, at TO, 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 TO varied between 13.1 ±
424 1.4 for water and 3.2 ± 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 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 t0, FO, and TO (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 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 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.

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

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

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

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

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

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

Capsules vs tablets.

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

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

Tablets adhered significantly less to the membrane than the capsules at the beginning of the 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, Δθ was first
495 constant. Then, it increased around 0.1 s to reach the front of the bolus (Δθ approx. +15°), or
496 a plateau around Δθ = 5°, 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 immerged in water (Shimasaki et al., 2019). Authors considered that the HPMC

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

Conclusions

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

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

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

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

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

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Ethical Statements

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

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

Data Availability Statement

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

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

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Tables

Table 1: Characteristics of the SODF used in this study.

SODF	Ingredients	Shape	Size	Aspect ratio	Tablet to bolus cross section	Calculated volume	Mass	Density

Capsule “Spiruline Biologique”	*Spirulina platensis* powder, HPMC capsule	Size 0	22 mm long 7.5 mm width	2.93	24.1 %	861 mm^3	0.59 g	0.7
Tablet “Spirulina Bio”	*Spirulina platensis* compressed powder	Oblate, scored	22 mm long 7 mm width	3.14	26.7 %	842 mm^3	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 ¶**
Oat extract L1	Front	Low	Moderate	Fast
Oat extract L3	Front	Moderate	No elongation	Moderate
TUC L4	Front	Moderate	No elongation	Moderate
PEO L3	Front	High	Shortening	Slow
Gloup L4	Front	High	No elongation	Moderate
PEO L1	Middle	Low	Moderate	Fast
Glycerol L1	Middle	Moderate	Moderate	Fast
TUC L3	Middle	Moderate	Moderate	Fast
Glycerol L3	Middle	High	No elongation	Slow
Water	Back	Low	High	Fast
TUC L1	Back	Low	High	Fast

761

† Front: Δ front at TO < 10°; Back: Δ front at TO > 50°;

‡ Low: between 0.4 and 0.6 mL; High: > 0.9 mL

§ Shortening: BL ratio at TO < 1; Moderate: BL ratio at TO between 1.1 and 1.6; High: BL ratio at TO > 1.6

¶ Fast: TO between 0.4 and 0.5 s; Slow: TO > 0.6 s

Figure legends

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

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

Figure 3: Filament thinning of (a) Oat extract L1, (b) PEO L1, (c) Oat extract L3, (d) TUC L3, (e) PEO L3, (f) Glycerol L3, (g) Gloup L4, (h) TUC L4. Representative pictures of each liquid carrier at t 0, t ¼ breakup, t ½ breakup, t ¾ breakup, and t breakup (value of t breakup for this specific sample is indicated on the image).

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

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

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

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

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

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

Figure 9: Bolus elongation at TO (ratio of the bolus length at t0) for the different liquid carriers alone (O, round label), or with a SODF (X, cross label), in relation to their shear viscosity at $\dot{\gamma}$ = 300 s-1. Empty circles indicate that the samples had a relaxation time λc ≥ 10 ms.

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

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

Figure 1

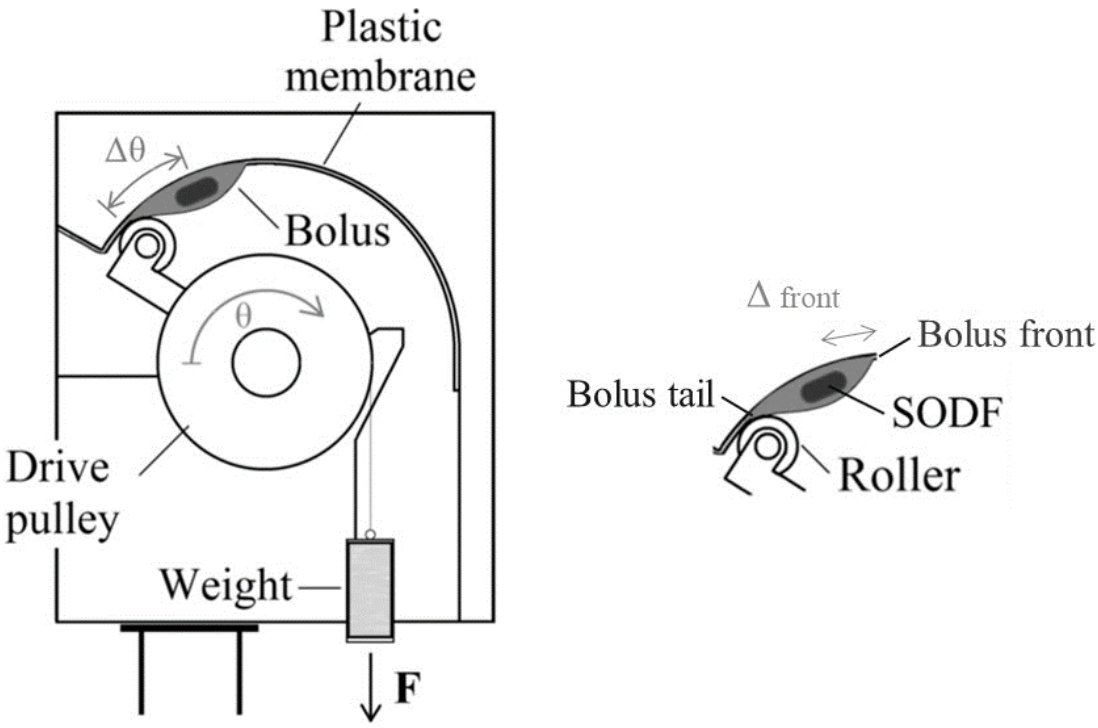
Plastic membrane
Δθ
Bolus
θ
Drive pulley
Weight
F
Δ front
Bolus front
Bolus tail
SODF
Roller

Figure 2

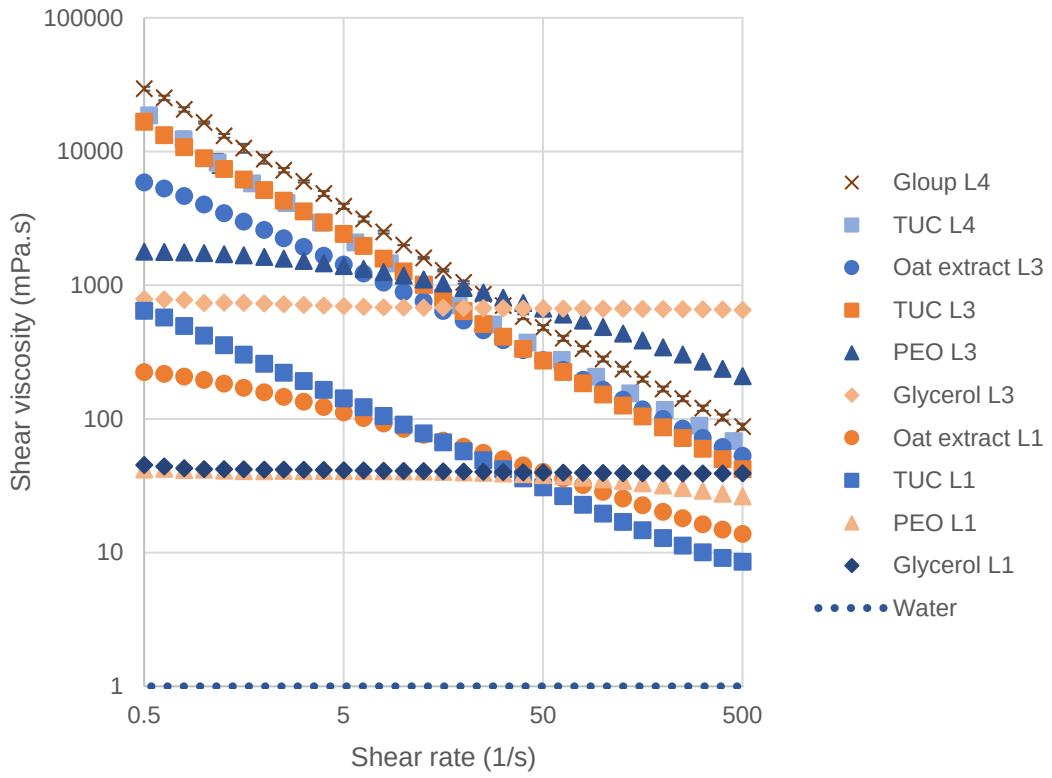
100000
10000
1000
100
10
1
Shear viscosity (mPa.s)
0.5
5
50
500
Shear rate (1/s)
Gloup L4
TUC L4
Oat extract L3
TUC L3
PEO L3
Glycerol L3
Oat extract L1
TUC L1
PEO L1
Glycerol L1
Water

Figure 3

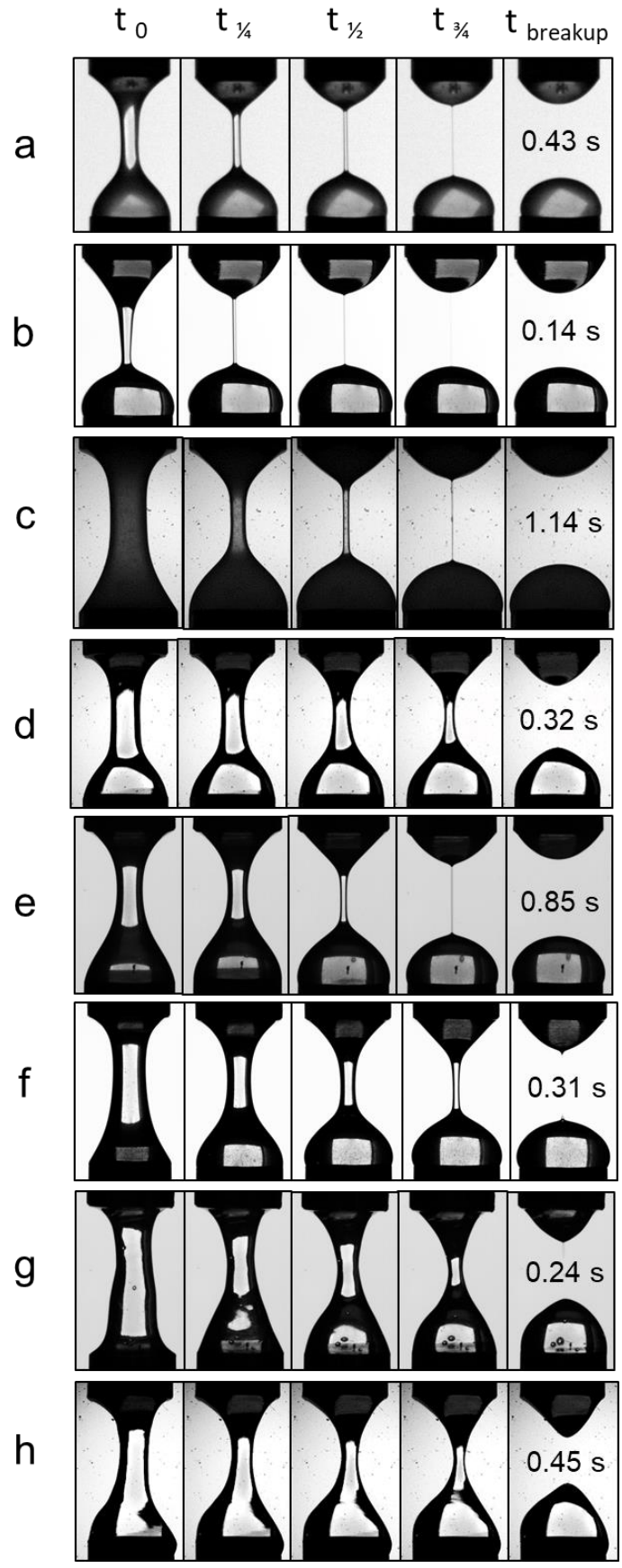
t 0
t ¼
t ½
t ¾
t breakup
a
0.43 s
b
0.14 s
c
1.14 s
d
0.32 s
e
0.85 s
f
0.31 s
g
0.24 s
h
0.45 s

Figure 4 a

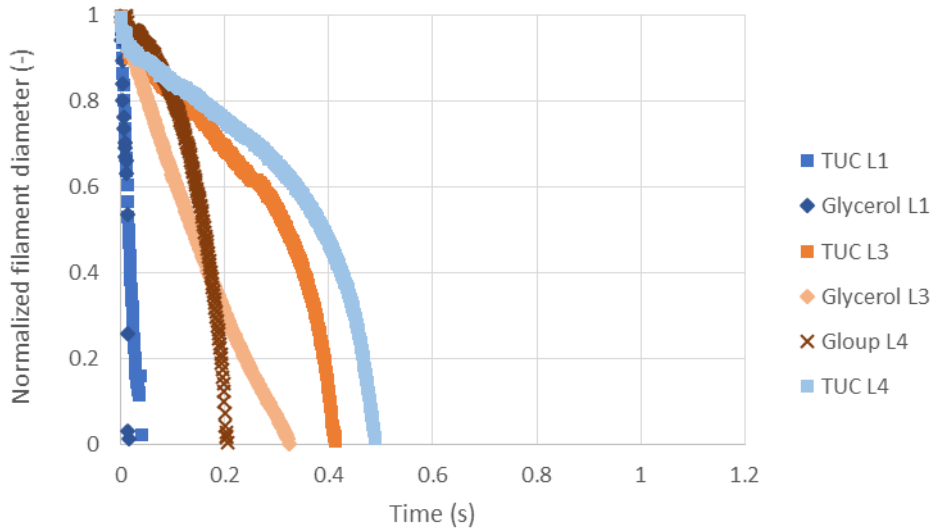

Figure 4 b

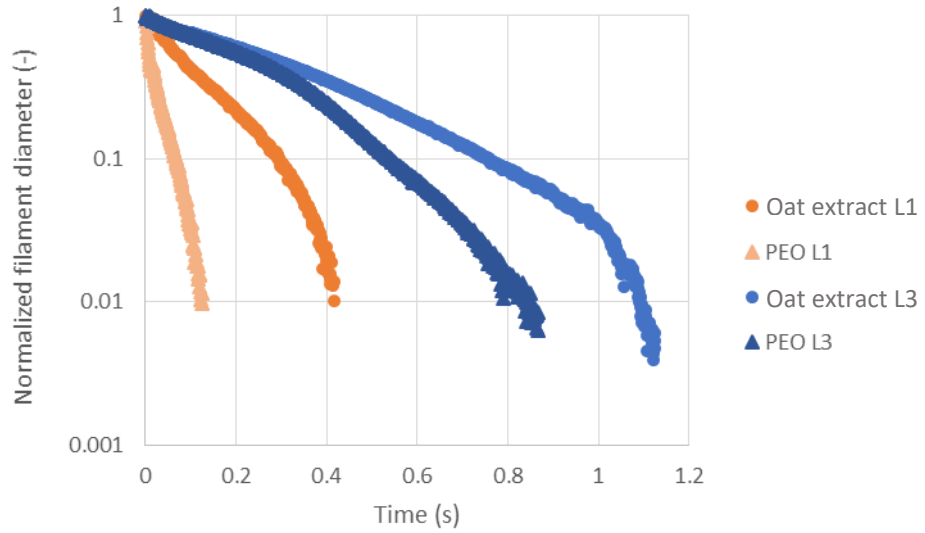

Figure 5

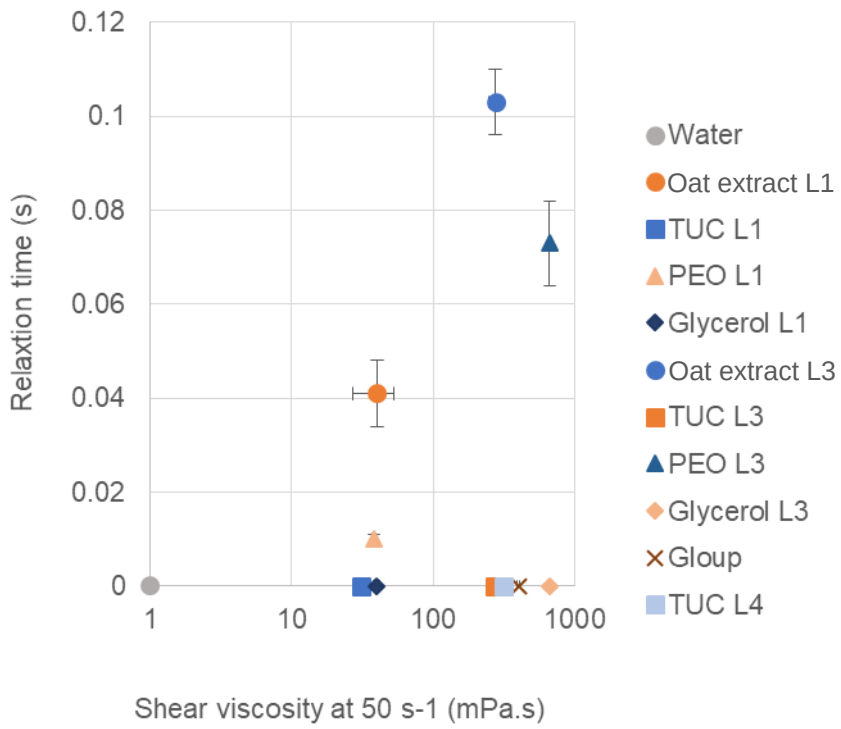
0.12
0.1
0.08
0.06
0.04
0.02
0
Relaxtion time (s)
1
10
100
1000
Shear viscosity at 50 s-1 (mPa.s)
Water
Oat extract L1
TUC L1
PEO L1
Glycerol L1
Oat extract L3
TUC L3
PEO L3
Glycerol L3
Gloup
TUC L4

Figure 6

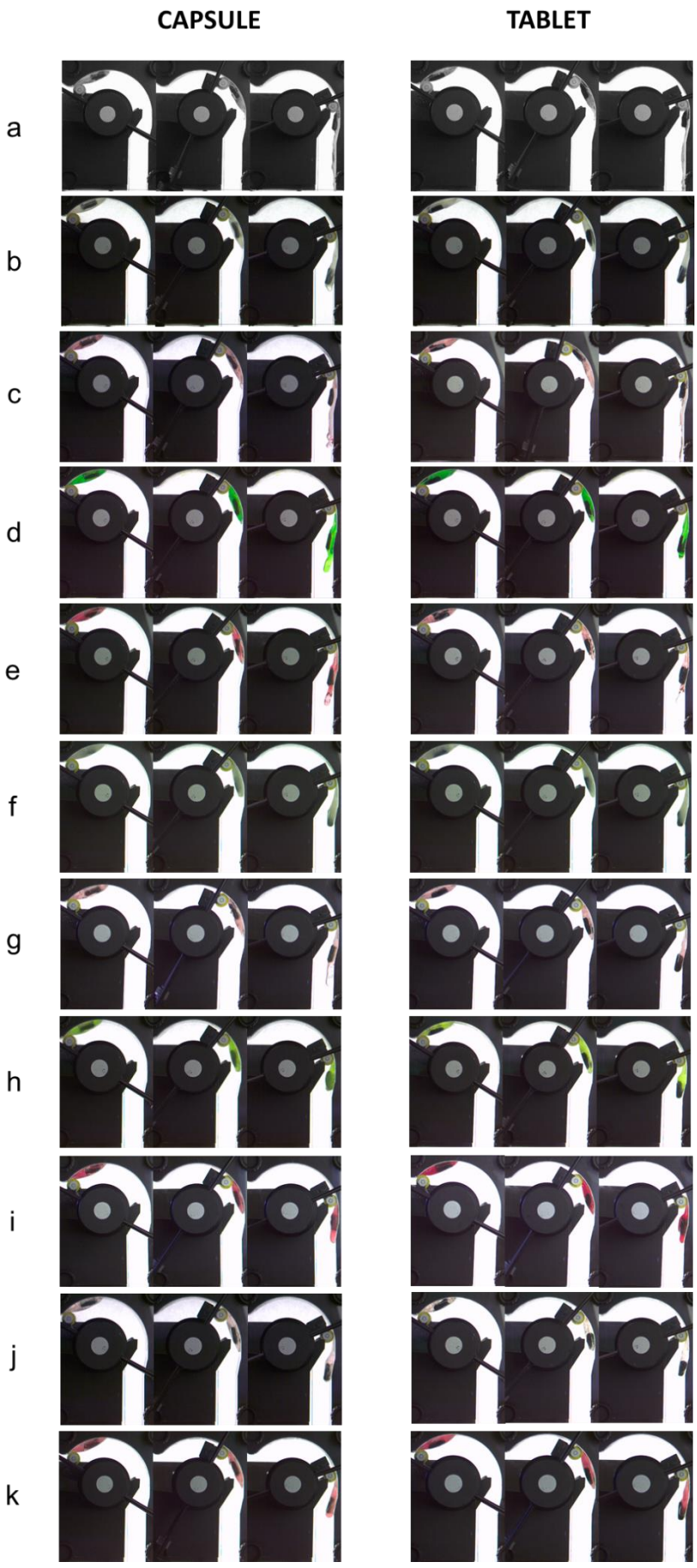

Figure 7

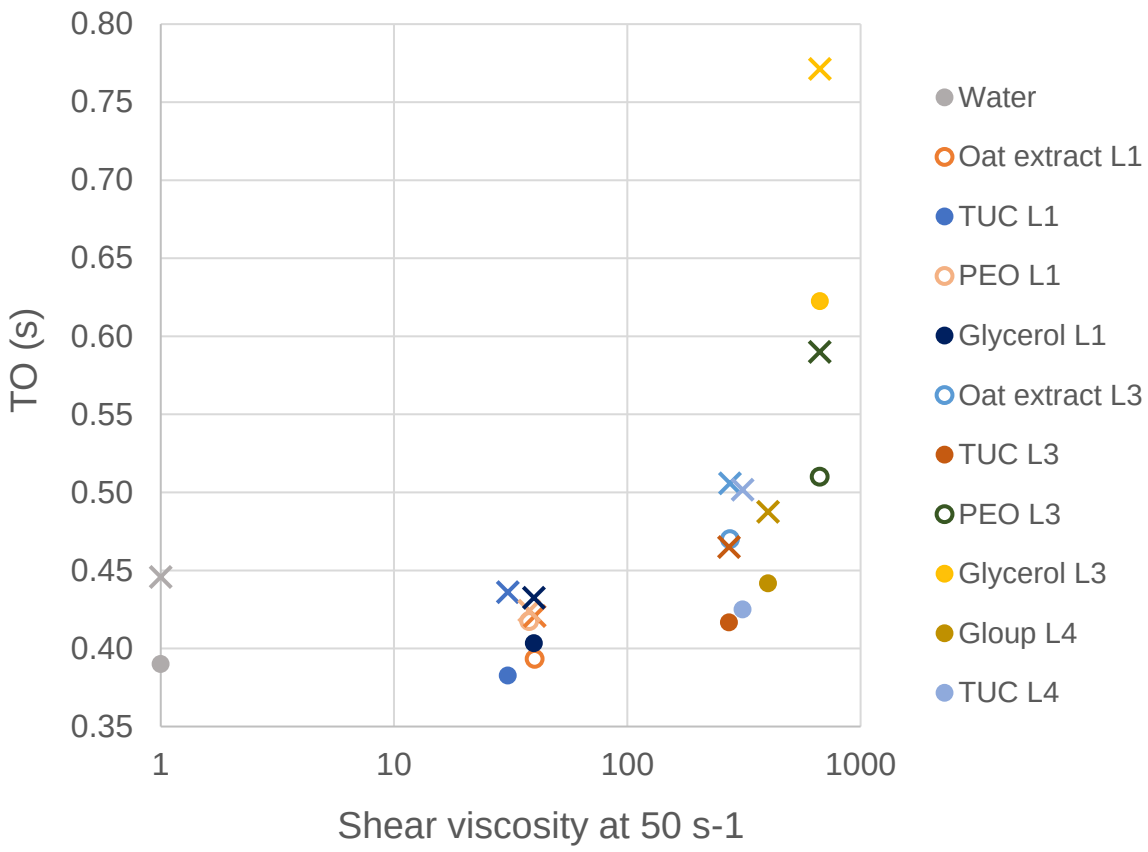
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
TO (s)
1
10
100
1000
Shear viscosity at 50 s-1
Water
Oat extract L1
TUC L1
PEO L1
Glycerol L1
Oat extract L3
TUC L3
PEO L3
Glycerol L3
Gloup L4
TUC L4

Figure 8

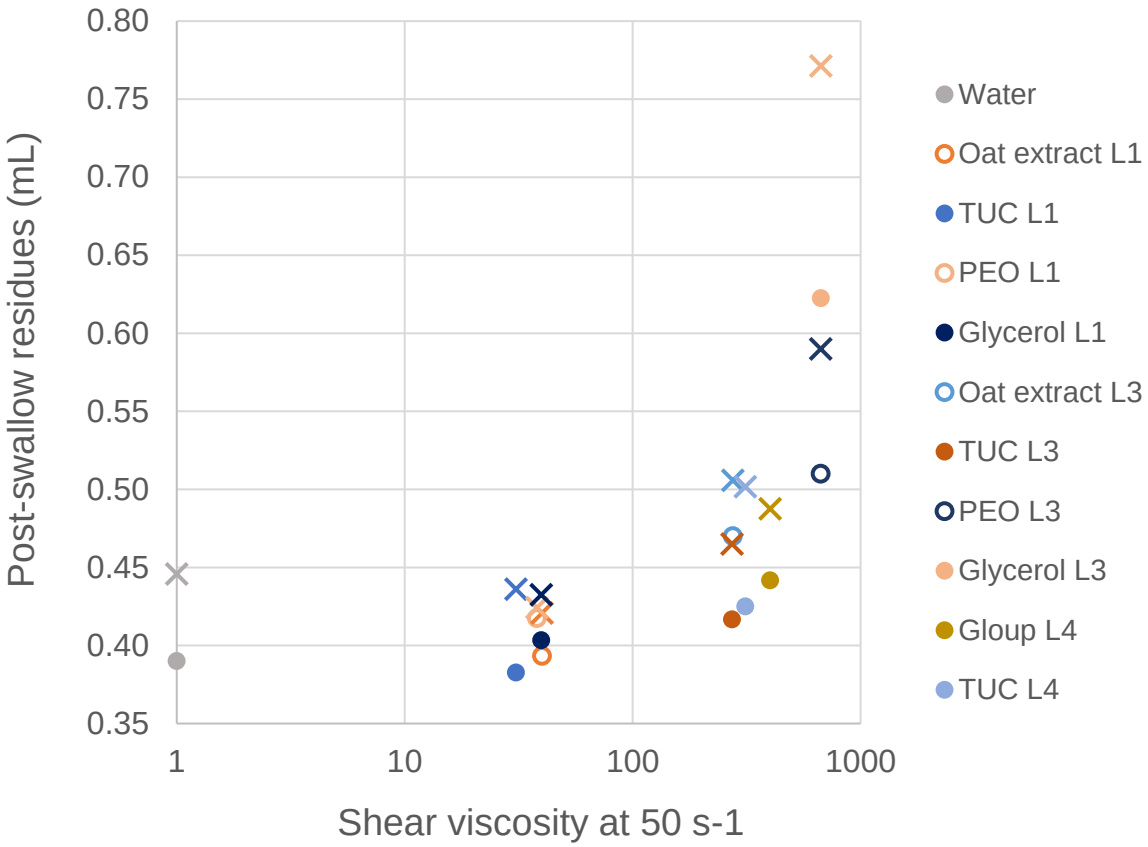
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
Post-swallow residues (mL)
1
10
100
1000
Shear viscosity at 50 s-1
Water
Oat extract L1
TUC L1
PEO L1
Glycerol L1
Oat extract L3
TUC L3
PEO L3
Glycerol L3
Gloup L4
TUC L4

Figure 9

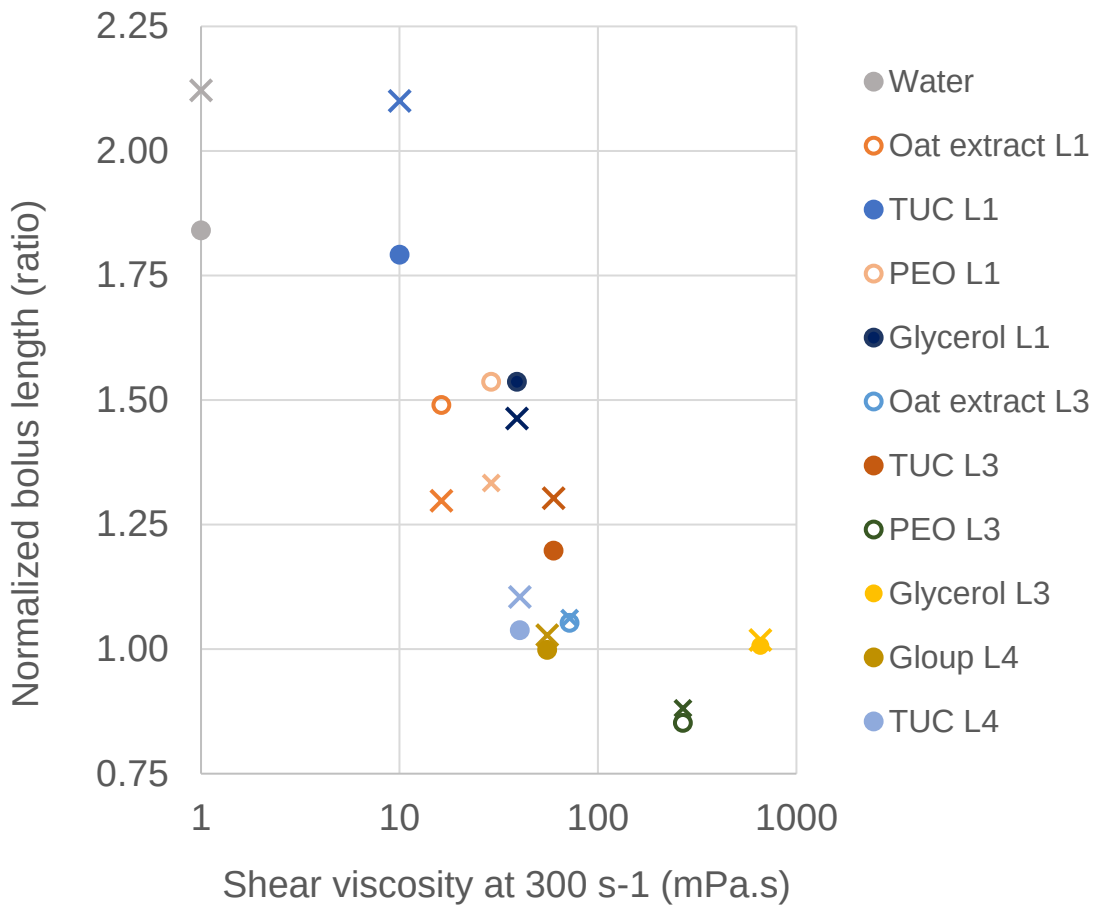
2.25
2.00
1.75
1.50
1.25
1.00
0.75
Normalized bolus length (ratio)
1
10
100
1000
Shear viscosity at 300 s-1 (mPa.s)
Water
Oat extract L1
TUC L1
PEO L1
Glycerol L1
Oat extract L3
TUC L3
PEO L3
Glycerol L3
Gloup L4
TUC L4

Figure 10

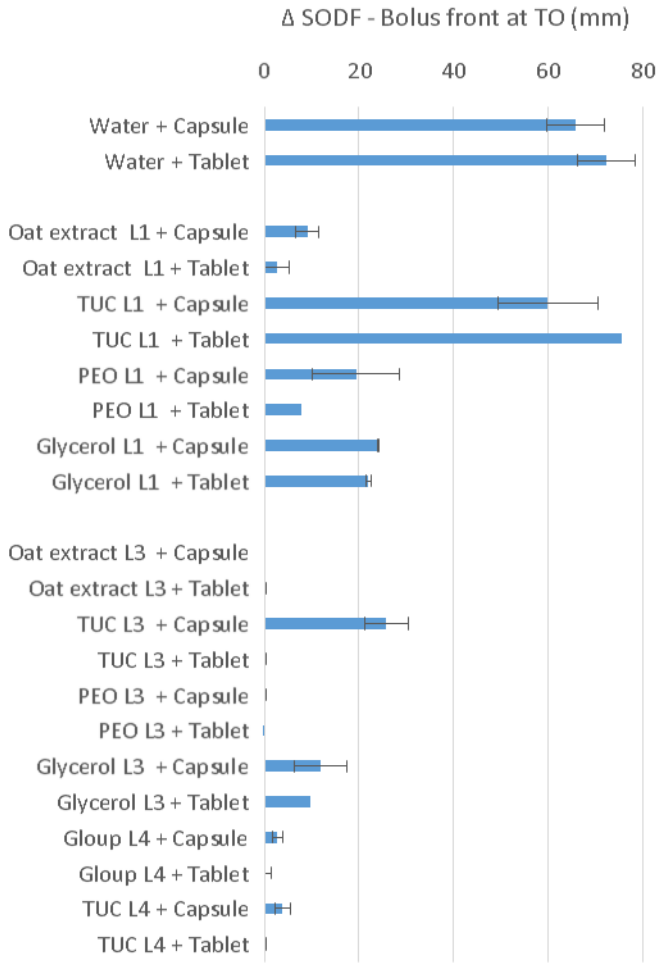
Δ SODF - Bolus front at TO (mm)
0
20
40
60
80
Water + Capsule
Water + Tablet
Oat extract L1 + Capsule
Oat extract L1 + Tablet
TUC L1 + Capsule
TUC L1 + Tablet
PEO L1 + Capsule
PEO L1 + Tablet
Glycerol L1 + Capsule
Glycerol L1 + Tablet
Oat extract L3 + Capsule
Oat extract L3 + Tablet
TUC L3 + Capsule
TUC L3 + Tablet
PEO L3 + Capsule
PEO L3 + Tablet
Glycerol L3 + Capsule
Glycerol L3 + Tablet
Gloup L4 + Capsule
Gloup L4 + Tablet
TUC L4 + Capsule
TUC L4 + Tablet

Figure 11 a

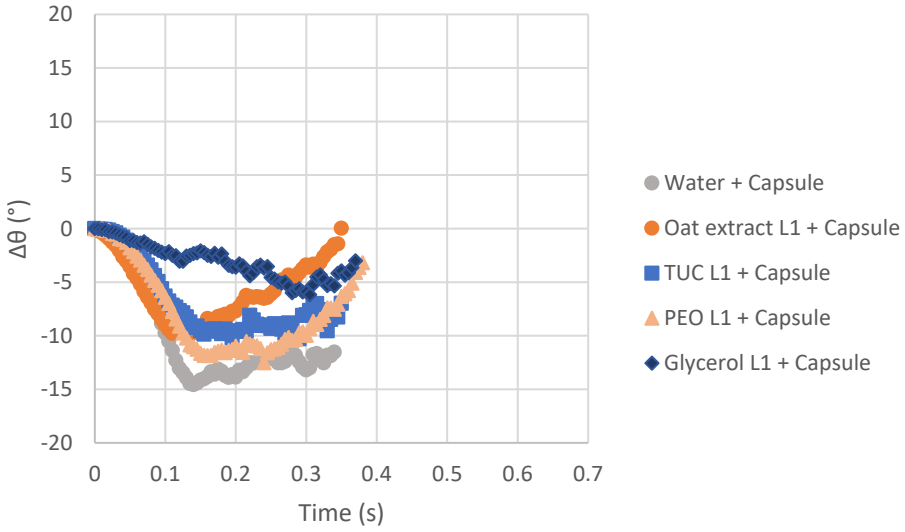

Figure 11 b

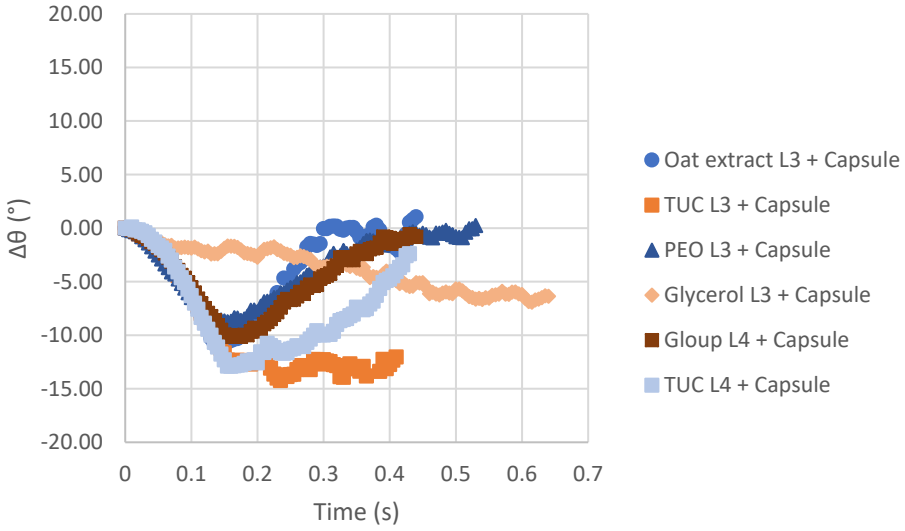

Figure 11 c

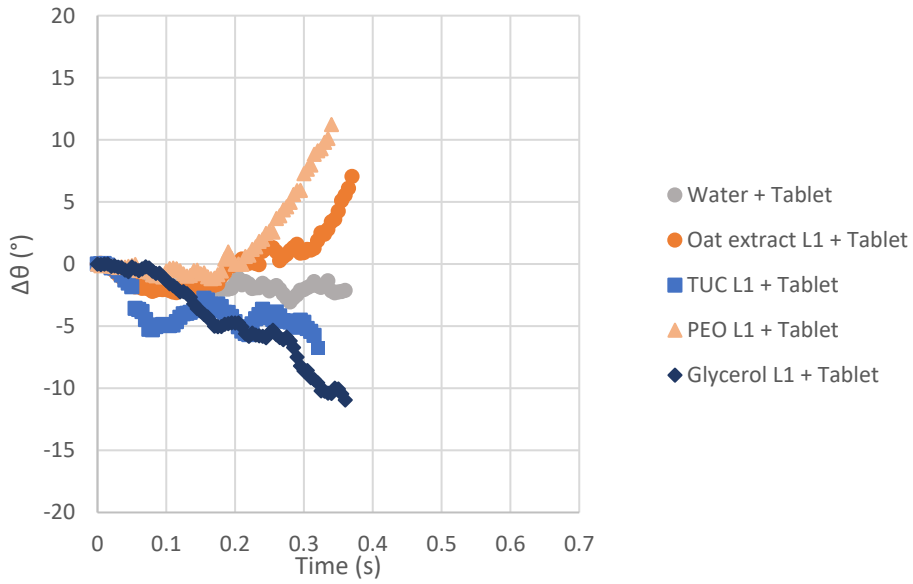

Figure 11 d