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Keywords

Soft robotics; swallowing; food carrier; flexible solid oral dosage forms; minitablet; size;

Highlights

- A novel soft robotic *in vitro* test inspired by the anatomy of a 2-year-old child was developed based on data from the literature
- Based on the *in vitro* results, semi-solid foods like yoghurt and apple puree may be considered more suitable than thin liquids for swallowing mini-tablets (MT).
- The reduction of MT size did not favour its *in vitro* swallowability in the range considered

- Spreading MT on top of a teaspoon full of carrier should be preferred to favour the *in vitro* MT swallowability.
- The volume fraction of MT could be increased up to 0.20 without influencing any aspect of swallowability in the *in vitro* conditions tested.

Acknowledgements

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ABSTRACT

Soft robotics could help providing a better understanding of the mechanisms underpinning the swallowability of solid oral dosage forms (SDOF), especially by vulnerable populations such as the elderly or children.

In this study a novel soft robotic *in vitro* device is presented, the Pediatric Soft Robotic Tongue (PSRT), inspired by the literature data on the anatomy and physiology of a 2-year-old child. Multi-particulate oral formulations (i.e., mini-tablets (MT)) were considered, including different scenarios such as SODF carrier (i.e., soft-food, liquid), administration methods, SODF size and volume fraction.

In vitro results showed that semi-solid foods like yoghurt and apple puree (shear viscosity above ~ 150 mPa.s at $\dot{\gamma}$ = 50 s^{-1}, and its yield stress up to ~ 5 Pa) may be considered more suitable than thin liquids (i.e., xanthan gum 0.25%) for swallowing MT. However, the reduction of MT size did not bring any benefit in terms of swallowability in the range studied. Regarding the administration method, spreading MT on top of a teaspoon full of carrier should be preferred over mixing MT with the carrier or placing MT on the tongue first to favour their swallowability. Finally, and under the in vitro conditions studied using yoghurt as carrier, it would be possible to increase the volume fraction of SODF up to 0.20 without influencing swallowability according to the three parameters evaluated (% of MT swallowed, bolus velocity, and post-swallow residues). These results should help to design more focused sensory and/or clinical tests to improve product formulation and patient acceptability.

INTRODUCTION

Children need age-appropriate pharmaceutical formats, specifically designed, developed, and evaluated for pediatric use (Mistry, Batchelor, and Uk 2017; Ternik et al. 2018). There, acceptability is particularly important to achieve better clinical outcomes, as well as improving the quality of life of young patients. According to the European Medicines Agency (EMA), acceptability assessment must be included in the pediatric pharmaceutical development program of new formulations and described in the pediatric investigation plan (Committee for Medical Products for Human Use and Paediatric Committee 2013). However, knowledge in this area is still limited, and different methodologies may be implemented due to uncertainties of regulatory requirements as no international consensus has been established yet (Ternik et al. 2018).

Acceptability can be defined as an overall ability of the patient and caregiver to use a medicinal product as intended or authorized (Kozarewicz 2014). The acceptability of oral dosage forms depends mainly on their palatability and swallowability, which can be evaluated during clinical trials in relevant patient populations. Concerning solid oral dosage forms (SODF), size and shape, taste and after taste, dose volume, and ease of administration are generally considered as critical acceptability attributes (Kozarewicz 2014; Walsh et al. 2018).

Tablets and capsules are not recommended for children under 6 years old because of swallowing difficulties and risk of choking. However, mini-tablets (≤ 4 mm in diameter), considered suitable for children between 2 and 5 years (European Medicines Agency 2013; Mistry et al. 2017), are particularly interesting as they combine the stability of SODF with the dosage flexibility of liquids (Mistry et al. 2017; van Riet-Nales et al. 2016). Several clinical studies with placebos have shown that 2 years old children not only are able to swallow a mini-tablet but was also preferred over alternative formulations like powders, suspensions, or syrups (Klingmann et al. 2013, 2015; Musiime et al. 2014; Riet-Nales et al. 2013; Spomer et al. 2012;

Thomson et al. 2009). However, large volumes are often required, and it is still unclear how many mini-tablets can be administered at once to a 2-year-old child, even if early studies have shown that young children can swallow several mini-tablets at a time (Klingmann et al. 2018; Kluk et al. 2015).

The administration method could also be determinant for the acceptability of such multi-particulate formulations. In clinical studies, single mini-tablets are generally placed on the child's tongue and accompanied by a drink of choice such as water, milk or juice (Klingmann et al. 2013; Spomer et al. 2012; Thomson et al. 2009), whilst larger amounts of minitablets (5 to 100) are mixed with soft foods like jelly, yoghurt or mashed fruits, and administered on a spoon (Klingmann et al. 2018; Kluk et al. 2015). Among soft foods, applesauce, yoghurt, and puddings are often recommended as swallowing-assistive vehicles (Freerks et al. 2020; Lee et al. 2019; Ternik et al. 2018), but literature demonstrating the suitability of these soft foods as carriers for young children is still limited. According to Kluk et al., (2015), the use of a jelly medium to swallow multiple mini-tablets avoided the spreading of units inside the oral cavity, helped deglutition, and protected children (2 to 3 years old) from choking. Similarly, Klingmann et al., (2018) reported that the administration of high numbers of mini-tablets with soft foods instead of drinks improved their acceptability by children between 2 and 5 years of age.

Currently, the swallowability of multi-particulate formulations is evaluated during clinical studies by direct observation of the child's mouth after administration (Bracken et al. 2019; Klingmann et al. 2013, 2015, 2018; Kluk et al. 2015; Münch et al. 2021; Spomer et al. 2012; Thomson et al. 2009) or from parents reports about problems experienced during administration at home (Musiime et al. 2014; Riet-Nales et al. 2013). Nevertheless, pharmaceutical companies need guidance to identify the key attributes that can improve swallowability before starting clinical trials in order to reduce iterations during product development and improve patient

104 safety (Kozarewicz 2014; Ternik et al. 2018). In this context, *in vitro* models of swallowing,
105 and particularly soft robotics, could help to clarify the mechanisms involved during SODF
106 swallowing by young children.
107 Different i*n vitro* models have already been used to elucidate the relations between the physical
108 properties of a bolus and its flow during the oral, pharyngeal, and oesophageal phases of
109 swallowing in adults (Marconati et al. 2019; Qazi and Stading 2019). Regarding pharmaceutical
110 formulations, previous works used an experimental setup called the "artificial throat" (Mowlavi
111 et al. 2016) to investigate the swallowing dynamics of a bolus with pellets (Marconati et al.
112 2019) and the dynamics of different combinations of liquid carriers and SODF, considering the
113 impact on swallowing of both shear and extensional rheology (Lavoisier et al. 2021, Marconati
114 et al. Food Function, 2020). This *in vitro* model reproduces the peristaltic motion induced by
115 the tongue during the oral phase of swallowing in adults, but it represents a strong simplification
116 of the shape of the oral cavity and the tongue, using rigid materials. A more realistic adult *in*
117 *vitro* swallowing model based on soft robotics has been recently developed (Marconati et al.
118 2020).
119 No *in vitro* models have been used yet to gain insights on SODF swallowing by young children,
120 due to the specific anatomical and physiological features.
121 To investigate the swallowability of multi-particulate pediatric oral formulations, this study
122 developed a soft-robotic *in vitro* device that, adapting the soft-robotic tongue proposed by
123 Marconati et al., (2020), reproduces the key features of the anatomy and swallowing physiology
124 of a 2-year-old child. This novel *in vitro* model has been used to investigate the swallowability
125 of mini-tablets under different scenarios: (i) testing the effect of semi-solid carriers (apple
126 puree, stirred yoghurt, and xanthan gum solutions), (ii) the effect of the size of the particles,
127 (iii) of their volume fraction in the bolus and finally, (iv) comparing different administration
128 methods (e.g., on the tongue, mixed with the carrier).

MATERIALS & METHODS

1. Materials

1.1 Carriers and insalivation ratio

This study considered two food carriers, apple puree ("Pomme nature", 100 g, Andros France SNC, Biars-sur-Cère, France) and stirred yoghurt ("Velouté yaourt nature brassé", 125 g, Danone SA, Paris, France). Three different concentrations of xanthan gum (0.25, 0.5, and 1 % w/v) in mineral water (Vittel) were also used (43708, xanthan from Xanthomonas campestris, Sigma-Aldrich, St. Louis, MO, USA). Each food carrier was diluted with artificial saliva (Brodkorb et al. 2019; Minekus et al. 2014) to mimic saliva incorporation during bolus formation in the mouth before swallowing. In this study the artificial saliva did not contain α-amylase. No information about saliva incorporation during bolus formation by toddlers was found in the literature, but salivary flows seem to be similar between 2 years old and adults (i.e., basal salivary flow rate (0.2-1 mL/min) and stimulated salivary flow rate (0.5-5 mL/min)) (Wollmer et al. 2022). Therefore, the amount of saliva incorporated when eating semi-solid food products was estimated with adult volunteers, and calculated according to Drago et al., (2011). Briefly, five healthy volunteers (31 ± 10 years old) took a teaspoon of apple puree or yoghurt, kept the product in mouth for 30 s, and spat it in a container. The ratio of saliva added in the bolus with respect to the wet food sample (h_w) was 0.23 ± 0.10, meaning that approx. 0.2 g of saliva were incorporated /g of semi-solid food. Based on these preliminary tests, the dilution ratio (carrier: artificial saliva) was fixed at 5:1.

1.2 Minitablets

All formulations were placebos. Minitablets of 1.8, 2.3, 2.5, and 3 mm in diameter were produced and provided by F. Hoffmann La Roche AG (Basel, CH). Minitablets were coated with Surelease® (E-7-7050, Colorcon, Darford, Kent, UK) to avoid swelling and solubilization during swallowing experiments. The density of the coated minitablets was 1.3 g/mL.

2. Rheological properties

The rheological properties of the carriers were assessed with a Modular Compact Rheometer 301 (Anton Paar GmbH, Graz, Austria) at 20°C. A concentric cylinder geometry (CC27) was used to measure the properties of the apple puree and XG samples, and a parallel-plate system (PP50, 1 mm gap) with a rough surface was used for yoghurt samples.

Shear viscosity of the carriers was evaluated by steady shear tests in a range of shear rates between 1 and 500 reciprocal seconds, and their yield stress was estimated through steady stress tests by increasing the shear stress from 0.01 to 30 Pa for all samples.

3. *In vitro* swallowing with the Pediatric Soft Robotic Tongue (PSRT)

A pediatric version of the soft robotic tongue proposed by Marconati et al., (2020) was developed to simulate the oral phase of swallowing of 2-year-old children. This model relies on physiological parameters from human studies available in the literature, as detailed in the following sections.

3.1 Oral cavity

The design of the oral cavity was adapted from a model of the oral airway constructed by Xi and Longest (2007) based on CT scans of a healthy adult and measurements reported in the literature. This model was modified to include the functionality of the tongue (Marconati et al. 2020). A smaller version of this 3D model was designed to stimulate the morphology of the oral cavity at 24 months by selecting relevant anatomical features and measurements from clinical studies on healthy children around this age reported in the literature (Figure 1a).

First, the distance between the inner side of the lips to the posterior wall of the pharynx reported by Bickmann et al., (2015) based on NMR/CT scans of children between 2 and 3 years old in Germany was considered as the length of the oral cavity (i.e., 58 mm). Then, the width of the back of the oral cavity (i.e., 35 mm) was considered as the width of the dental arch between the mandibular 2nd molars measured by Foster, Hamilton, and Lavelle (1969) on the primary

dentition of British children between 2 ½ and 3 years old. Finally, the values extracted by Vorperian (2005) from observations by MRI of the hard and soft tissue vocal tract structures of 2 years old children in Wisconsin (USA), and particularly the hard and soft palate lengths, were considered as a representative measure of the arc length of the oral cavity (ie., 66 mm).

The top of the oral cavity was pierced with 4 holes located at 1, 5.8, 22.8 and 44.8 mm from the tongue tip along the sagittal direction. Two large holes with 1/8" metallic nuts glued on top were used to tightly screw pressure transducers to record the dynamic evolution of palatal pressure during swallowing tests of liquid samples. The last two were used as feeding holes: a large one (14 mm diameter) to feed small solids like mini-tablets or foods containing large particles (hermetically sealed with a rubber stopper during the swallowing tests), and a small one (4 mm diameter) where a plastic tube was fitted and used to fed liquids from a syringe pump. The oral cavity was 3D printed in a transparent material (VeroClear® resin) to allow bolus movement observation during swallowing.

3.2 Soft robotic tongue

A soft actuator was designed by Marconati et al., (2020) to reproduce the peristaltic movement of the tongue. This soft robotic tongue was made up of two air chambers that can be inflated and deflated independently to reproduce key lingual functions: bolus containment prior to swallowing, and bolus propulsion during the oral phase of swallowing. The shape obtained during a swallowing test has been compared qualitatively against *in vivo* ultrasound imaging of the tongue (Mowlavi et al. 2016). The tongue was produced by casting silicone rubber (Smooth-On Eco-flex 00-30) mixed with 0.5% w/w of a nonionic surfactant (sorbitan mono-oleate, Span 80, CAS: 1338-43-8, from Sigma Aldrich) in a mold. Mechanical properties and wettability were similar to the human tongue (Marconati et al. 2020). This soft actuator was adapted to mimic the tongue of a 2-year-old child by scaling down the adult model to obtain a pediatric

soft tongue of 46 mm length and 18 to 32 mm, proportional to the pediatric oral cavity previously designed (Figure 1b).

3.3 Swallowing pattern

The soft robotic tongue control system previously developed by Marconati et al., (2020) was used, with slight modifications to better simulate relevant physiological features of the swallowing pattern at 24 months. According to Potter, Nievergelt, and VanDam (2019) the maximum tongue strength of 3 years old children is approx. 20 kPa (no data has been reported in the literature for younger children). Since the tongue strength used during swallowing is around 40% of the maximum tongue strength (Ferris et al. 2016; Park, Oh, and Chang 2016; Rommel et al. 2006), the maximal pressure applied against the palate should be around 8 kPa in the PSRT. The target inflation pressures for the anterior and posterior chambers of the tongue were adjusted accordingly. Various studies have shown that swallowing coordination and oropharyngeal transit time are similar between healthy adults and young children (Almeida et al. 2008; Frakking et al. 2017; Rommel et al. 2006, 2014), therefore, the actuation sequence described by Marconati et al., (2020) with no delay between the deflation of the posterior chamber and the inflation of the anterior chamber (t_A = 0 ms) was chosen.

3.4 In vitro swallowing conditions

The volume of food typically swallowed by 2-year-old children is considered to be 5 mL (Jones and Work 1961; Vaiman, Segal, and Eviatar 2004). MT were therefore administered with 5 mL of carrier. To study the effect of the administration method on the swallowability of the formulations three different configurations were used: (1) MT were mixed with the carrier in the oral cavity (2.5 mL of the carrier fed first and MT spread on top before feeding the last 2.5 mL), (2) MT were directly spread on the tongue before adding the 5 mL of carrier, and (3) MT were mixed with the 5 mL of carrier in a beaker and fed together to ensure an homogeneous

distribution of MT in the bolus. A first swallow, with the studied carrier only, was performed before to lubricate the oral cavity. Swallowing tests were done at room temperature (ca. 20°C).

3.5 *Measured variables*

Swallowed MT (%)

The number of particles successfully swallowed during the *in vitro* swallowing test was monitored. MT were counted by visual examination of the swallowed bolus. Results are expressed in terms of percentage of total MT initially fed.

Bolus velocity (s)

The velocity of the bolus was measured during the swallowing test. A high-speed camera (model ac A2040-120 um, Basler, Ahrensburg, Germany) was used to record the bolus transit at 150 frames per seconds. The characteristic oral transit time was defined as the time required for the bolus front to exit the oral cavity (bolus FO).

Carrier residues (%)

Residues left in the oral cavity after the swallowing test were also monitored. The container receiving the sample propelled out of the PSRT was weighted before and after the test. The amount of carrier residues left in the oral cavity was calculated as follow:

$$m_{residues} = m_{sample\ fed} - m_{sample\ swallowed} \quad (1)$$

$$m_{carrier\ residues} = m_{total\ residues} - m_{particles\ left\ in\ the\ cavity} \quad (2)$$

Results are expressed in terms of percentage of total carrier initially fed.

Palatal pressure (kPa)

The dynamic evolution of palatal pressure (mid and post-palate) during swallowing tests was recorded by two piezoresistive pressure sensors (model PX2AG2XX002BAAAX from Honeywell, MN, USA) housed in the holes of the rigid palate. These sensors were used to determine the pressures involved in the *in vitro* oral transit of the carriers. Results are expressed as a relative pressure in kPa.

4. Adhesion measurements

A TAHD Texture Analyzer (Stable Micro Systems, Surrey, UK) with a 500 g load cell was used to measure the adhesion between a MT coated with Surelease and the surface of the silicon tongue described in section M&M 3.2. The MT was fixed to a 2 cm diameter compression platen probe using double-sided adhesive tape, while the tongue was fixed on the lower platform of the instrument.

To study the effect of the carriers on the adhesion between the MT and the tongue, 30 µL droplets of the target carrier were placed on the top of the tongue surface before testing; this amount of liquid fully covered the MT during testing.

The 'hold until time' mode was used with five seconds of holding time making contact, a test-speed of 1 mm/s, a maximum compression force F_{max} of 0.05 N, and a trigger force of 0.005 N (Figure 2). The study was carried out at room temperature. Adhesion force was quantified as the hysteresis upon retraction of the MT from the tongue. Adhesion measurements were carried out over three different locations on the silicon tongue per sample, with at least three compressions per location.

5. Statistical analysis

Results are shown in terms of the mean ± SD. The Kruskall-Wallis test on ranks was used to study differences among samples. Conover-Iman test was then used to determine the significant differences between samples ($p < 0.05$). All analyses were performed with XLSTAT statistical software (version 2020.3.1.27, Microsoft Excel, Adinsoft, Paris, France).

RESULTS AND DISCUSSION

1. Rheological properties of the carriers

The rheological properties of the semi-solid carriers were investigated since they influence the ability of maintaining particles in suspension, the palatability (or mouthfeel), and the swallowability of multi-particulates (Kluk and Sznitowska 2014; Lopez et al. 2016; Steele et al. 2015). Flow curves obtained in steady shear are presented in Figure 3a.

In adults, the shear rates ($\dot{\gamma}$) during human swallowing have been estimated to be in a range between 1 s^{-1} in the mouth, and up to 1000 s^{-1} in the pharynx (Gallegos et al. 2012; Nishinari et al. 2016). The shear rheology of texture modifiers and food products is commonly reported at $\dot{\gamma}$ = 50 s^{-1}. Oral shear rates for 2-year-old are unknown, and there is no consensus on the shear rates most representative of food oral processing in infants and young children (Makame, De Kock, and Emmambux 2020; Steele et al. 2015; Sukkar et al. 2018).

All the samples showed a shear thinning behaviour (i.e., viscosity decreased rapidly with increasing shear rate) in the whole range of shear rates studied (1 – 500 s^{-1}). The XG suspensions had a more pronounced shear thinning behavior than the food carriers. The apple puree diluted with artificial saliva and XG 1 % had similar shear viscosities at $\dot{\gamma}$ = 50 s^{-1} (587 ± 14 and 460 ± 59 mPa.s, respectively); the yoghurt diluted with artificial saliva and XG 0.5 % had similar shear viscosities at $\dot{\gamma}$ = 50 s^{-1} (209 ± 5 and 167 ± 1 mPa.s, respectively). Compared to Newtonian fluids like syrups, shear thinning fluids require less efforts in oral processing and swallowing (Steele et al. 2015) but could also be less effective in "masking" the presence of particles in the mouth as their viscosity decreases under the relatively high shear rates experiences during oral processing (Steele et al. 2015).

The yield stress values estimated for the different carriers are presented in Figure 3b. The yield stress is the force required to break down the internal structure of a material for flowing (Cichero and Lam 2014; Zargaraan et al. 2013). It provides valuable information about the

effort needed to swallow a bolus: when τ_0 increases the tongue force necessary to make the carrier flow will also increase (Cichero and Lam 2014; Malouh et al. 2020). The XG suspension 1 % had the highest estimated τ_0 (12.2 ± 0.9 Pa) and XG 0.25 % the lowest (0.9 ± 0.2 Pa). Intermediate τ_0 were found for XG 0.5 % and the food carriers diluted with artificial saliva (between 2 and 5 Pa).

2. Mini-tablets swallowability *in vitro*

2.1 Effect of the type of semi-solid carrier on mini-tablets swallowability in vitro

The carriers detailed in section 1.2 were used to swallow 64 MT of 3 mm in diameter, which corresponds to a particle volume fraction of 0.20. Here, MT were mixed with the carrier in the oral cavity (i.e., administration method (1) cf. section M&M 3.4). The *in vitro* swallowing results are presented in Figure 4, and images of the PSRT containing the bolus (MT + carrier) before triggering the swallow are shown in Figure 5.

Overall, high success rates were reached with more than 75 % of the MT successfully swallowed (Fig. 4a) but differences were observed depending on the rheological properties of the carriers. A lower number of MT were swallowed with XG 0.25 % in these conditions (77 ± 7 %). This carrier had a low shear viscosity (ca. 60 mPa.s at $\dot{\gamma}$ = 50 s^{-1}), and a low yield stress (0.9 Pa). Consequently, MT were able to sediment in the bolus during the initial part of the test and were positioned on the tongue when the swallow was triggered (Fig. 5c). Interactions between the artificial tongue and MT, such as adhesion, may affect the swallow of the particles. Moreover, it has been shown *in vitro* that low viscosity fluids are not the most efficient carriers for SODF as they tend to flow faster than the particles which lag behind the liquid bolus (Lavoisier et al. 2021; Marconati et al. 2018).

With XG 0.5 % and the yoghurt diluted with artificial saliva, MT also sedimented on the tongue (Fig. 5d) but the effect was much reduced, and almost all the MT were successfully swallowed

(≥ 90 %). These two carriers had higher shear viscosities and yield stresses (η 167 and 209 mPa.s at $\dot{\gamma}$ = 50 s^{-1} and τ_0 of 4.1 and 2.4 Pa, respectively) than XG 0.25 %.

When swallowed with XG 1 % and the apple puree diluted with artificial saliva, very high success rates were also reached (≥ 90 %). In this case, the shear viscosity of the carriers was too high for the MT to sediment in the bolus (η between 460 and 590 mPa.s at $\dot{\gamma}$ = 50 s^{-1}) (Fig. 5e). Interestingly, the apple puree gave better results than XG 1% (96 ± 2 % against 90 ± 2 %, respectively), which may be caused by the XG 1% high yield stress (4.5 for the apple puree vs. 12.2 for XG 1 %) or the slightly higher viscosity of apple puree at shear rates above 100 s^{-1}.

These results are consistent with a previous study (Marconati et al. 2019) in which a critical viscosity threshold for smooth swallowing was observed both *in vivo* and *in vitro*. Differences between carriers above η = 45 mPa.s at $\dot{\gamma}$ = 50 s^{-1} did not result in a significant improvement of multi-particulates palatability and oral transport. Similarly, (Lopez et al. 2018) observed *in vivo* that multi-particulates were easier to swallow when they were dispersed in polymeric hydrogels compared to water. No significant differences were found between hydrogels with different rheological properties (η between 70 and 1150 mPa.s at $\dot{\gamma}$ = 50 s^{-1}), even if participants reported differences in terms of mouthfeel perception and tended to prefer samples with thin and middle-range consistencies as opposed to thicker samples (Lopez et al. 2018).

Bolus velocity and post-swallow residues were not influenced by the type of carrier used. Bolus FO was measured between 0.16 and 0.19 s (Fig. 4b) which is coherent with the physiological duration of the oral phase of swallowing (i.e., < 0.5 s) (Almeida et al. 2008; Frakking et al. 2017; Rommel et al. 2006, 2014). Carrier post-swallow residues were low, between 5 and 10 % of the initial amount of carrier fed (Fig. 4c), which indicates that all sample boluses were effectively transported and ejected during the swallowing tests. Finally, the maximum relative pressures in the oral cavity were measured mid-palate between 8 and 10 kPa and were not influenced by the type of carrier used (Appendix Fig. A).

According to these results, the *in vitro* swallowing tests performed with the novel Pediatric Soft Robotic Tongue (PSRT) showed physiologically relevant oral transit times and palatal pressures for 2-year-old children. Regarding multiple MT swallowability, results suggest that increasing the shear viscosity of the carrier above ~ 150 mPa.s at $\dot{\gamma}$ = 50 s^{-1}, and its yield stress up to ~ 5 Pa, can improve MT transport without decreasing the bolus velocity nor increasing post-swallow residues. Semi-solid foods such as apple puree and yoghurt therefore appear as suitable carriers to help MT swallowing in young children.

2.2 Effect of the size of the mini-tablets on their swallowability in vitro

Swallowing of multi-particulates as well as the feeling of residual particles in the mouth seem to increase with particle size (Marconati et al., 2019). In this section, diluted yoghurt with artificial saliva was used as a carrier to swallow MTs of different sizes (1.8, 2.5, and 3 mm in diameter), keeping a particle volume fraction constant of 0.20. MT were mixed with the carrier in the oral cavity (i.e., administration method (1) cf. section M&M 3.4). Results of these swallowing tests are presented in Figure 6.

Overall, neither the percentage of MTs swallowed nor the post-swallow residues were influenced by the diameter of the MTs (FIG. 6a and 6c, respectively), yet bolus front out time decreased from 0.19 to 0.16 s when the MTs size increased from 1.8 to 3 mm (Fig. 6b). The inclusion of a large number of solid particles in the liquid carrier modifies the rheological properties of the resulting suspension (Mueller, Llewellin, and Mader 2010), which can influence the dynamics of swallowing (Marconati et al. 2018).

According to these results *in vitro*, reducing the size of MT did not improve swallowability for a fixed particle volume fraction. Furthermore, when using smaller MT, a higher number of particles is needed to reach a specific volume/dose which may be more complicated to manipulate for parents or caregivers. Therefore, MT with an intermediate diameter (i.e., 2 to 3 mm) seem to be a good compromise to conciliate swallowability and practicability.

2.3 Effect of the particle volume fraction on mini-tablets swallowability in vitro

The effect of different particles volume fraction in the bolus (from 0.05 to 0.40) was studied with 2.5 mm MT and yoghurt diluted with artificial saliva. MT were mixed with the carrier in the oral cavity (i.e., administration method (1) cf. section M&M 3.4). The different particle volume fractions used in this section are presented in Table 1. Results of these swallowing tests are presented in Figure 7.

Table 1. MT volume fraction and bolus mass used in the present study.

MT volume fraction	MT number (d. 2.5 mm)	MT mass (g) (d. 2.5 mm)	Total bolus volume (mL)
0.05	22	0.34	5.26
0.10	46	0.72	5.55
0.15	74	1.15	5.89
0.20	104	1.62	6.25
0.25	139	2.17	6.67
0.30	178	2.78	7.14
0.35	224	3.49	7.70
0.40	278	4.34	8.34

As expected, increasing the volume fraction of MT (and the total volume of bolus swallowed) resulted in a decrease in the percentage of MT successfully swallowed, and in an increase of post-swallow residues (FIG. 7a and 7c, respectively). From 0.05 to 0.20 particle volume fraction, a very high success rate was observed (≥ 90 %), whilst bolus velocity was not impacted (bolus FO between 0.18 and 0.20 s) and post-swallow residues were low (≤ 15 %). From 0.35

387 particle volume fraction (3.49 g of MT, 7.70 mL of total bolus), the percentage of MT
388 swallowed decreased strongly and success rate fall under 75 %.
389 According to these results, it would be possible to increase the MT volume fraction up to 0.20
390 without influencing swallowability. However, the acceptability threshold should be evaluated
391 by a sensory panel to evaluate mouthfeel sensations such as grittiness (Imai, Hatae, and
392 Shimada 1995). Data in published literature demonstrating the acceptability of large quantities
393 of multi-particulates administered with semi-solid foods with a calibrated dosing spoon are
394 lacking. Klingmann et al., (2018) studied the acceptability and swallowability of multiple
395 uncoated MT in toddlers (i.e., 2 to 5 years old). They administered an entire dose of a maximum
396 of 400 MT with a soft food or a drink of the child's choice on a teaspoon. This number of MT
397 would equate with a drug dose of approx. 500 mg of a drug, allowing for the administration of
398 up to 80 mg/kg per day of the active drug. If we considered that the 400 MT of 2 mm diam.
399 were administered with 5 mL of carrier, it corresponds to a 0.25 particle volume fraction. The
400 authors reported that this was the upper limit of acceptability for toddlers, which is quite
401 consistent with our results, obtained with 2.5 mm MT.

402 *2.4 Effect of the administration method on mini-tablets swallowability in vitro*

403 The effect of the administration method on MT swallowability was studied with 2.5 mm MT, a
404 particle volume fraction of 0.20, and yoghurt diluted with artificial saliva as carrier. Three
405 different configurations were used: MT were either (1) spread on the carrier in the oral cavity,
406 (2) spread on the tongue before feeding the carrier, or (3) mixed with the carrier before feeding
407 (cf. section M&M 3.4). Results of these swallowing tests are presented in Figure 8.
408 The percentage of MT swallowed decreased significantly when the MT were placed on the
409 tongue (from 90 % with the administration method 1 to 61 % with method 2, Fig. 8a), whilst
410 both bolus velocity and post-swallow residues were not influenced (Fig. 8b and 8c,
411 respectively). This may be due to adhesion between the MT and the artificial tongue impeding

412 their flow with the carrier (cf. section R&D 2.5) or to an unfavorable position of the MT in the
413 bolus (i.e., carrier flowing on top of the MT). The percentage of MT swallowed was even lower
414 when the MT were previously mixed with the carrier (50 % with the administration method 3,
415 Fig. 8a), decreasing bolus velocity (Fig. 8b) and increasing the amount of post-swallow carrier
416 residues left in the *in vitro* oral cavity (Fig. 8c). This fact could be likely related to the
417 homogeneous distribution of the MT in the carrier that would increase the contact area available
418 between MT and the *in vitro* oral surfaces, increasing adhesive interactions, and reducing
419 swallowability consequently. These results suggest that MT should not be placed on the tongue
420 of the child first, and that MT should rather be spread on top of a spoonful of carrier than mixed
421 with the carrier in its container. Clinical studies are however necessary to confirm these
422 recommendations based on *in vitro* observations.

423 *2.5 Adhesion between mini-tablets and the artificial tongue*

424 Unintended adhesion of SODF to oral surfaces (e.g., mucosal tissue, tongue, teeth) is an
425 important aspect that should be considered during pediatric drug development to improve
426 swallowability (Drumond and Stegemann 2018). The results presented in the previous
427 paragraph suggest that adhesive interactions between the MT and the artificial tongue may
428 affect the percentage of MT swallowed *in vitro* (cf. section R&D 2.1 & 2.4). Therefore,
429 adhesion phenomena between a MT coated with Surelease® and the surface of the silicone
430 tongue in the presence of different carriers were further investigated (air and water were used
431 as a reference). Adhesion results are presented in Figure 9.
432 The strongest adhesion forces between the MT and the artificial tongue were measured in air
433 (4.3 ± 0.5 mN) and water (3.1 ± 1.3 mN). The presence of the artificial saliva reduced the
434 adhesion force between the MT and the artificial tongue (1.2 ± 0.6 mN). Pailler-Mattei et al.,
435 (2015) studied the adhesive interactions involved between a rigid indenter and *ex vivo* tongues
436 of young pigs (ca. 1 year) in the presence of human saliva and salivary substitutes. They

437 reported that bio-adhesive properties of the salivary substitutes were similar to human saliva,
438 and they were ranged between 0.2 and 1 mN depending on the type of saliva used. Those values
439 are fairly close to the adhesion force measured in this work, however, direct comparison is not
440 possible due to differing testing conditions (e.g., applied force, probe speed, probe size, volume
441 of wetting fluid, contact time).
442 The presence of food carriers reduced the adhesion between the MT and the artificial tongue,
443 except for XG 0.25%, which showed adhesion forces similar to those measured in water (Fig.
444 9). Adhesive interactions may therefore have hindered the swallowability of MT with XG
445 0.25% (cf. section R&D 2.1). The stronger MT sedimentation with XG 0.25% may also
446 contribute to this poor swallowing performance.
447 Finally, we observed that the apple puree tended to reduce the adhesion force slightly more than
448 the yoghurt (Fig. 9). This could justify the trend in swallowability presented in Figure 4a,
449 although the differences observed for these two carriers were not significant. This may be
450 related to the different composition and structure of these two products, which can influence
451 their adhesion and spread on the tongue surface (Dresselhuis et al. 2008; Fan, Annamalai, and
452 Prakash 2021), as well as affect the specific energy of the solid-liquid interface.

453 *2.6 Limitations and perspectives for future studies*

454 In this paragraph the limitations of this study will be described, also in view of identifying
455 interesting future research directions. In this study, the yoghurt and apple puree were diluted
456 with a relevant amount of water to imitate the insalivation ratio measured in adults *in vivo*. It
457 was also verified that the rheology of these two soft foods is not affected by the contact with
458 salivary amylase (unpublished data). However, the presence of a salivary lubrication layer was
459 not considered, nor its peculiar rheological properties. Considering these aspects is certainly an
460 interesting research direction for the future. Similarly, the PSRT could be improved by
461 considering the natural roughness induced by the tongue's papillae, taking inspiration by some

462 recent *in vitro* tribology studies (Andablo-Reyes et al. 2020; Mantelet et al. 2020; Srivastava et
463 al. 2021; Wang, Zhu, and Chen 2021).

464 **CONCLUSIONS**

465 A soft robotic *in vitro* model, was developed to investigate the oral phase of swallowing of
466 multi-particulate pediatric oral formulations, based on the anatomical and physiological data
467 available in the literature for 2-year-old children. The *in vitro* swallowing tests performed with
468 this novel Pediatric Soft Robotic Tongue (PSRT) showed oral transit times, post-swallow
469 residues, and palatal pressures physiologically relevant for 2-year-old children. The
470 swallowability of multiple mini-tablets (MTs) was investigated under different realistic
471 conditions: type of carrier, administration method, MT size, and particle volume fraction.
472 According to our findings, semi-solid foods with a shear viscosity of at least ~ 150 mPa.s at a
473 shear rate of 50 s^{-1} and an intermediate yield stress (2-5 Pa) at 20°C are suitable as assistive
474 vehicles for MTs, facilitating drug transport without affecting neither bolus velocity nor post
475 swallow residues. At a particle volume fraction of 0.2, the size reduction of MTs from 3 mm to
476 1.8 mm did not improve swallowability. When increasing MT volume fraction (from 0.05 to
477 0.4), up to 0.2 no significant impact was observed on the *in vitro* swallowing. However, the
478 acceptability threshold should be further evaluated by a sensory panel, considering mouthfeel
479 sensations and grittiness. The distribution of the MTs in the carrier strongly affects the
480 percentage of MTs swallowed, and these *in vitro* results suggest that MTs should not be placed
481 on the tongue nor fully mixed with the carrier, but they should rather be spread on top of the
482 carrier to facilitate swallowing. These findings may help to design more effectively follow-up
483 clinical or sensory studies to determine SODF acceptability threshold and to improve the
484 formulation of the products
485

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Figures captions :

Figure 1: (a) 3D model of the oral cavity prototype, and (b) schematic sectional view of the soft robotic tongue developed to study the oral phase of swallowing of 2 years old children (dimensions in mm).

Figure 2: Test used to measure the adhesion between a MT coated with Surelease and the surface of the soft robotic tongue.

Figure 3: (a) Shear viscosity as a function of shear rate for the different carriers and (b) yield stress of the different carriers.

Figure 4: (a) % of MT swallowed, (b) bolus velocity (s), (c) % of carrier residues depending on the semi-solid carrier used. Red letters indicate significant differences ($p < 0.05$).

Figure 5: Initial position of the MT (64 MT , 3 mm in diameter) before an *in vitro* swallow. Arrows indicate the position of the MT in the bolus.

Figure 6: (a) % of MT swallowed, (b) bolus velocity (s), (c) % of carrier residues depending on the size of the MT. Red letters indicate significant differences ($p < 0.05$).

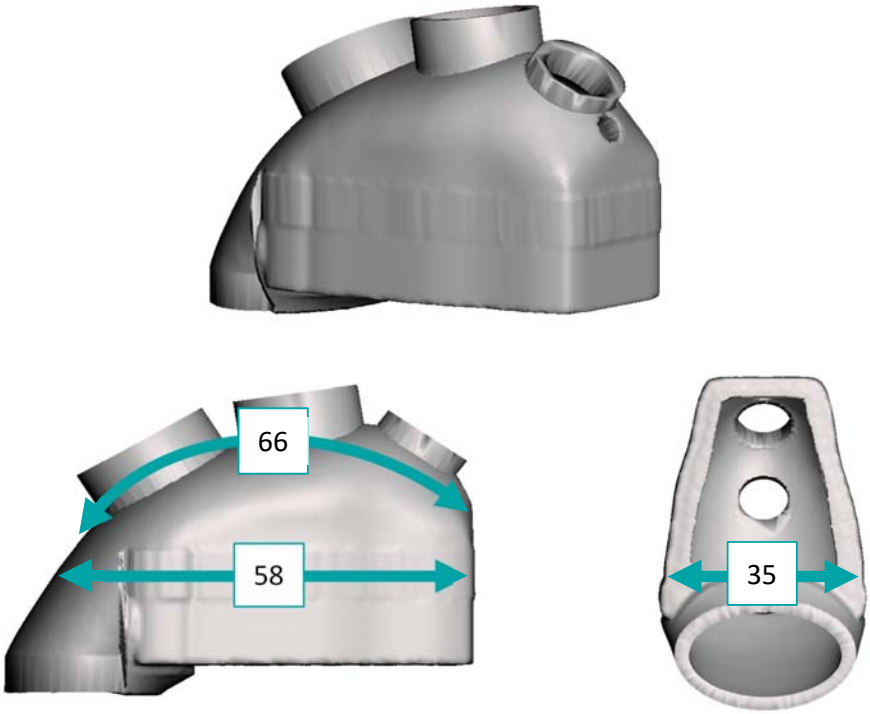
Figure 7: (a) % of MT swallowed, (b) bolus velocity (s), (c) % of carrier residues depending on the particle volume fraction. Red letters indicate significant differences ($p < 0.05$).

Figure 8: (a) % of MT swallowed, (b) bolus velocity (s), (c) % of carrier residues depending on the administration method. Red letters indicate significant differences ($p < 0.05$).

Figure 9: Adhesion force between the MT and the artificial tongue as a function of the carrier used. Adhesion measurements in air and water are used as reference. Red letters indicate significant differences ($p < 0.05$).

Figure 1

(a)


66
58
35

(b)

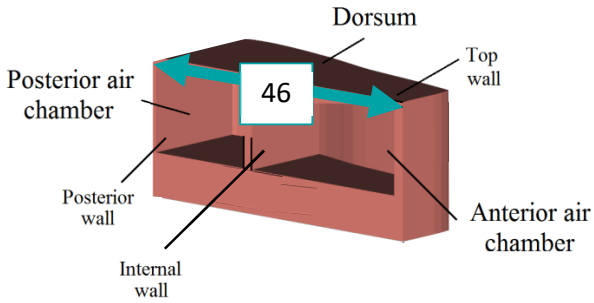
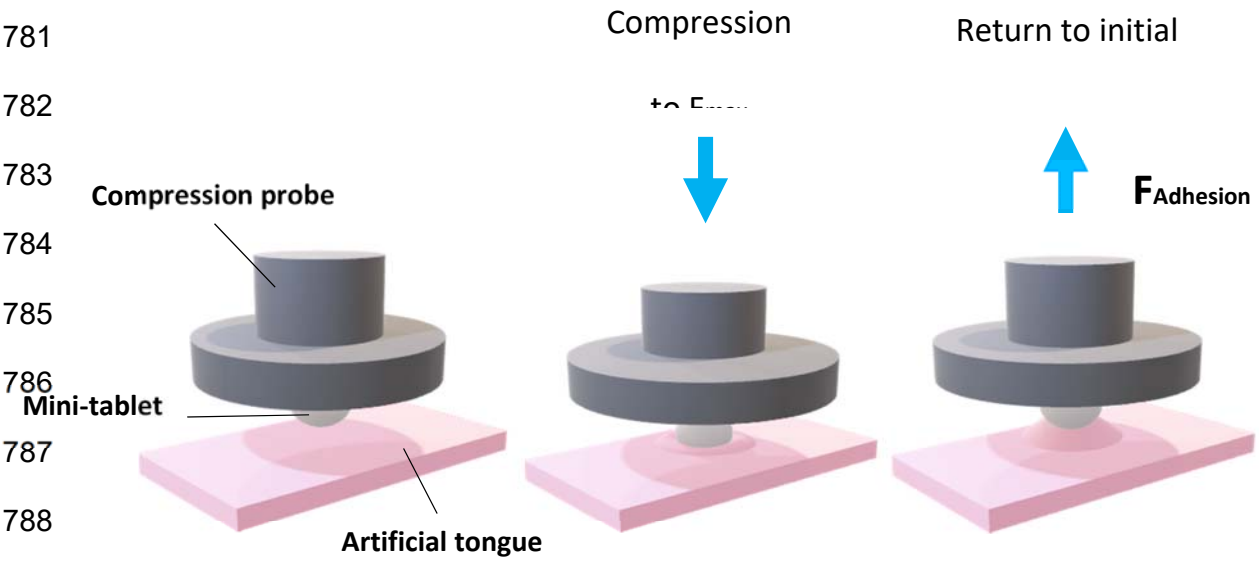

Dorsum
Top wall
Posterior air chamber
46
Posterior wall
Anterior air chamber
Internal wall

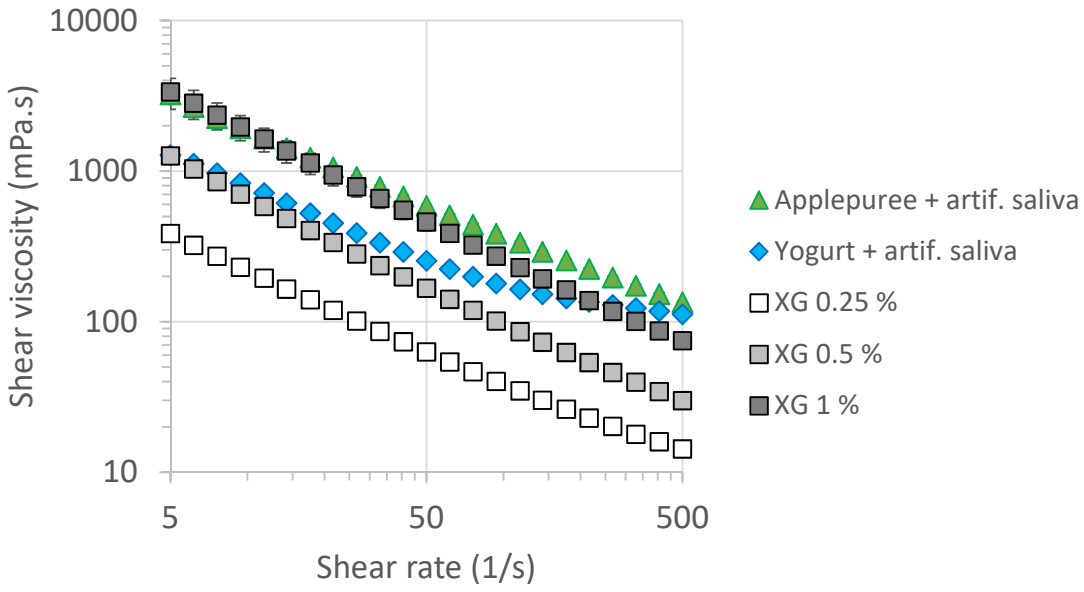
Figure 2


Compression
Return to initial
Compression probe
FAdhesion
Mini-tablet
Artificial tongue

794 Figure 3

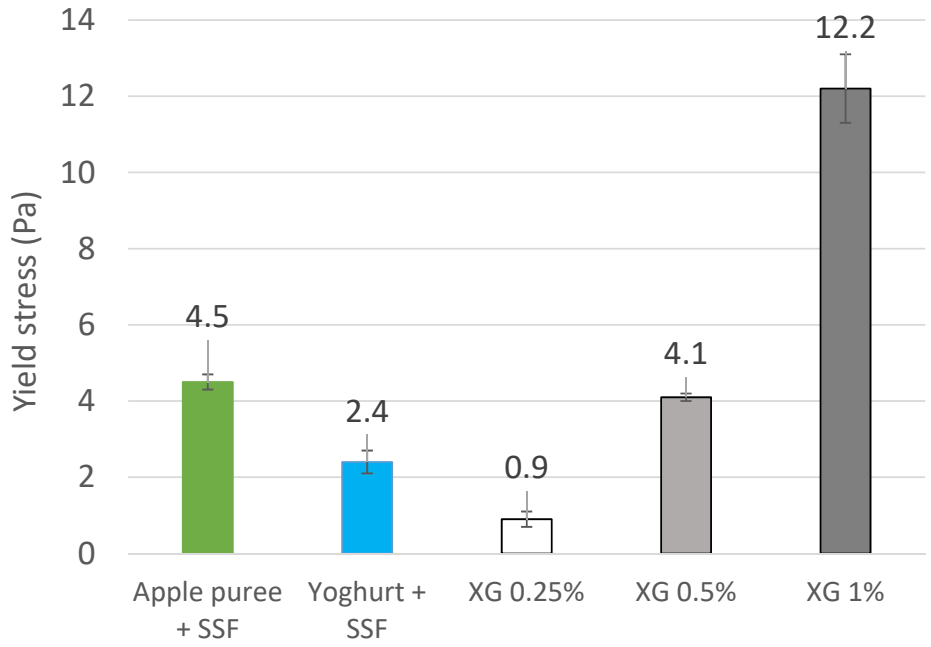
795

796 (a)



797

798 (b)

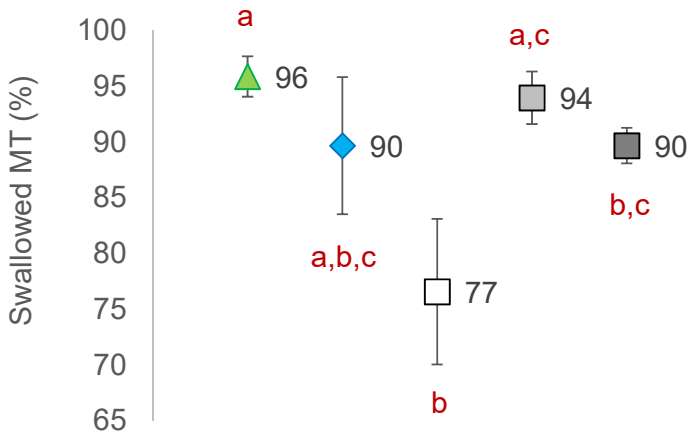


799

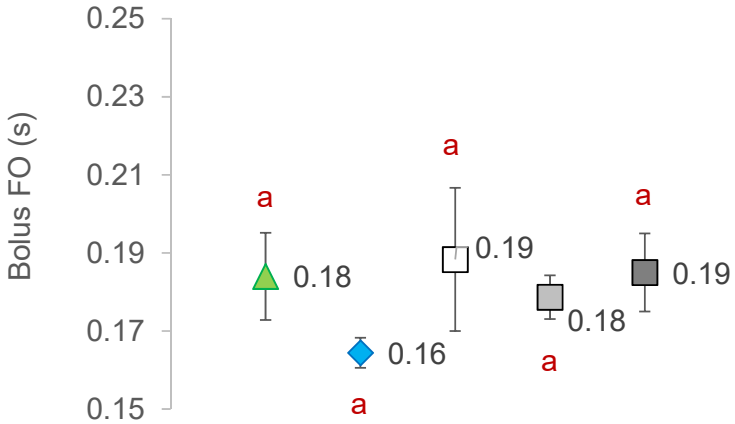
800

Figure 4

(a)


Swallowed MT (%)
100
95
90
85
80
75
70
65
a
96
90
a,b,c
77
b
a,c
94
90
b,c

(b)


Bolus FO (s)
0.25
0.23
0.21
0.19
0.17
0.15
a
0.18
0.16
a
a
0.19
a
a
0.18
a
a
0.19

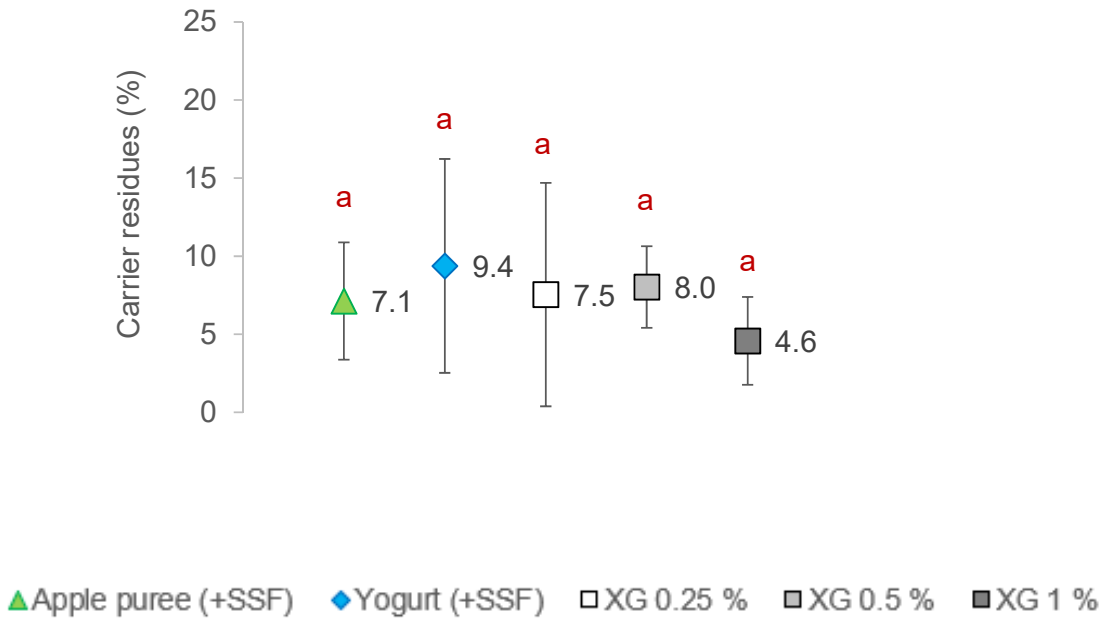
811

812

813

814 (c)

815

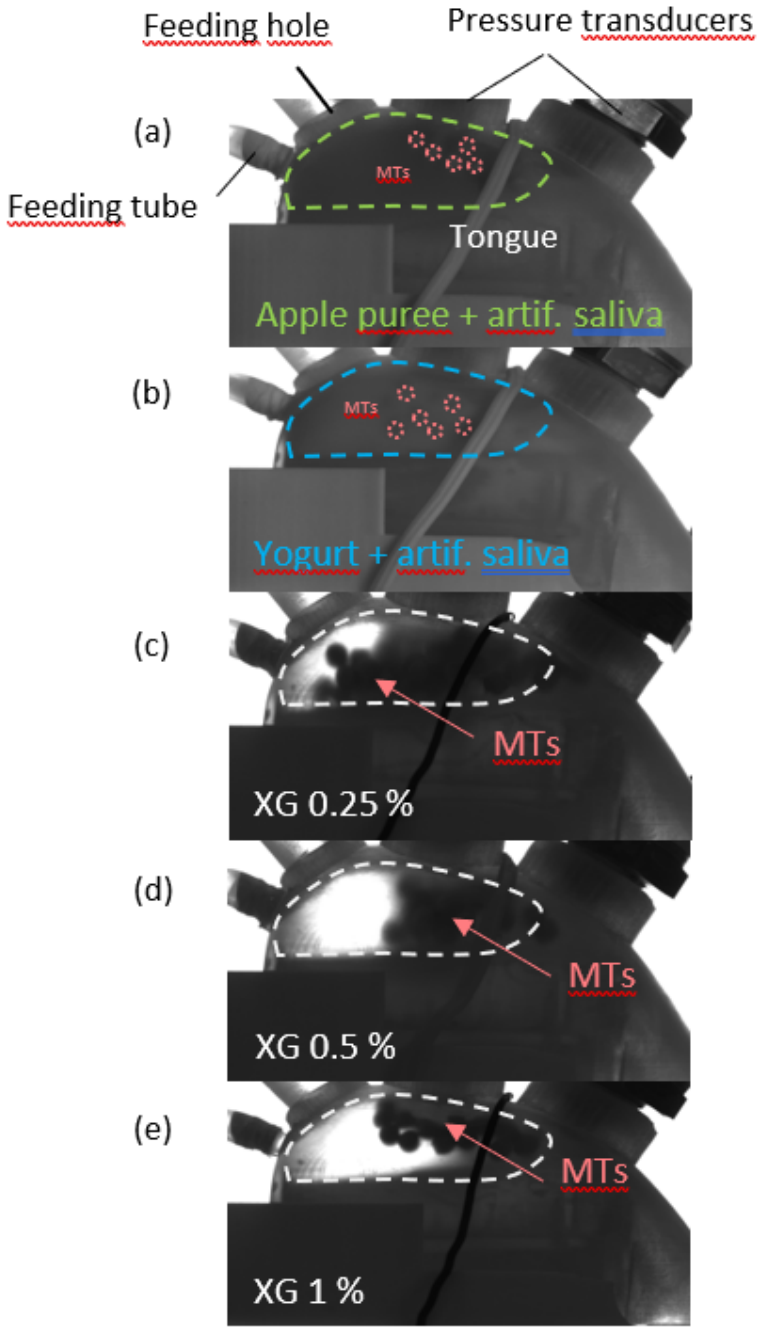


816

817

818

819 Figure 5

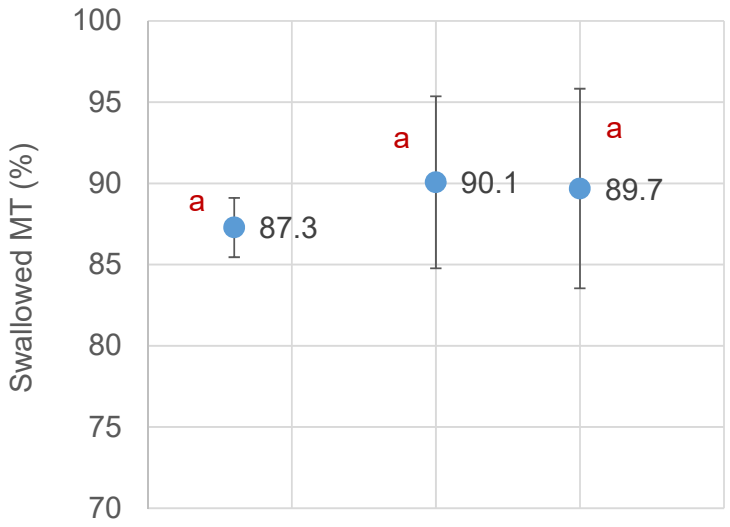


820

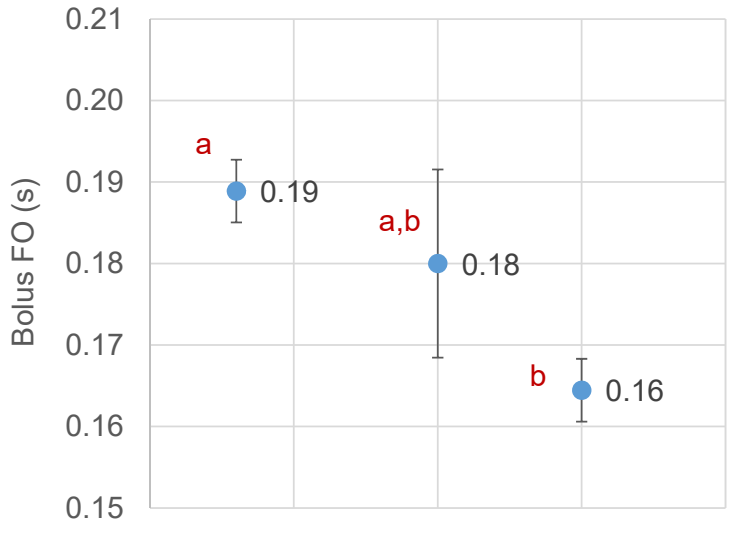
821

Figure 6

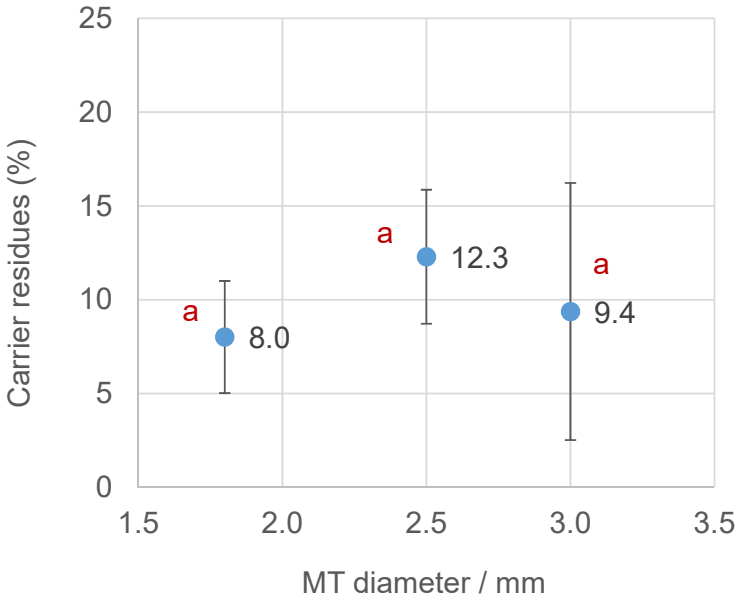
(a)


Swallowed MT (%)
100
95
90
85
80
75
70
a
87.3
a
90.1
a
89.7

(b)


Bolus FO (s)
0.21
0.20
0.19
0.18
0.17
0.16
0.15
a
0.19
a,b
0.18
b
0.16

(c)



829

830

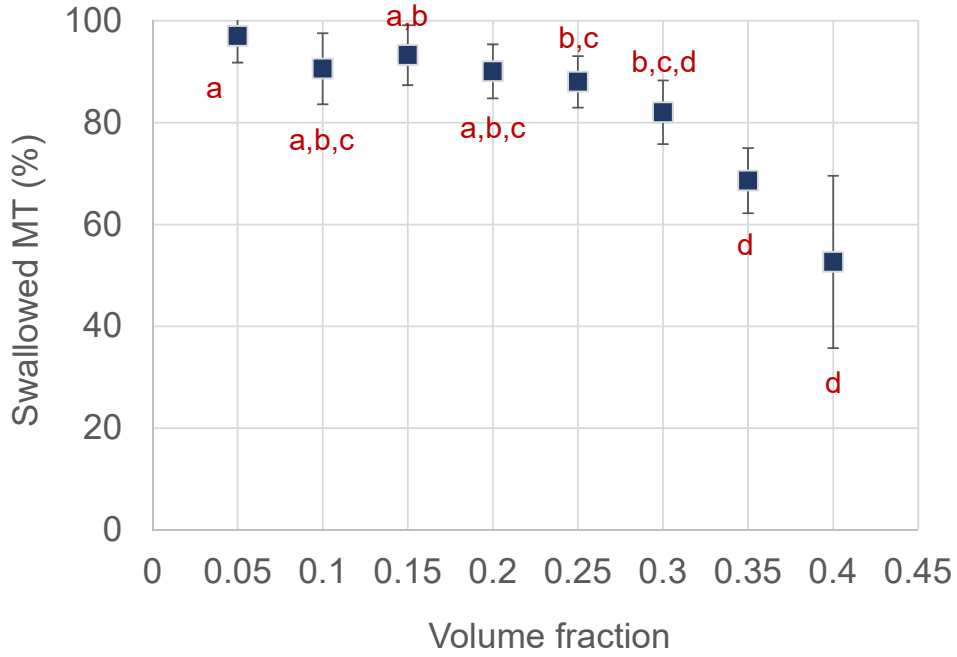
831

832

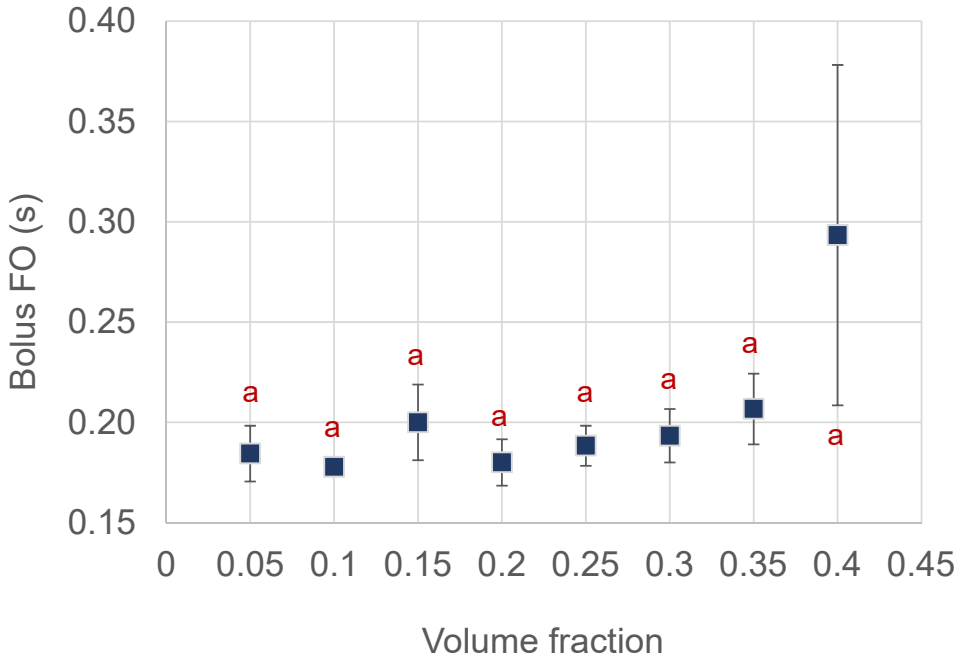
833

Figure 7

(a)

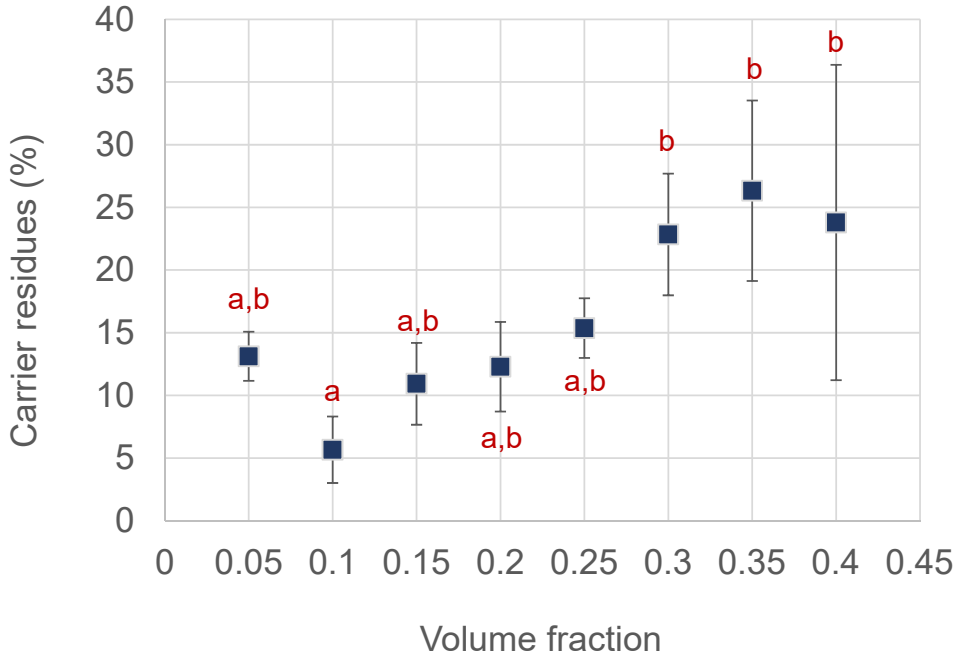

Swallowed MT (%)
100
80
60
40
20
0
a
a,b,c
a,b
a,b,c
b,c
b,c,d
d
d
0
0.05
0.1
0.15
0.2
0.25
0.3
0.35
0.4
0.45
Volume fraction

(b)


Bolus FO (s)
0.40
0.35
0.30
0.25
0.20
0.15
a
a
a
a
a
a
a
a
0
0.05
0.1
0.15
0.2
0.25
0.3
0.35
0.4
0.45
Volume fraction

840

841 (c)



852

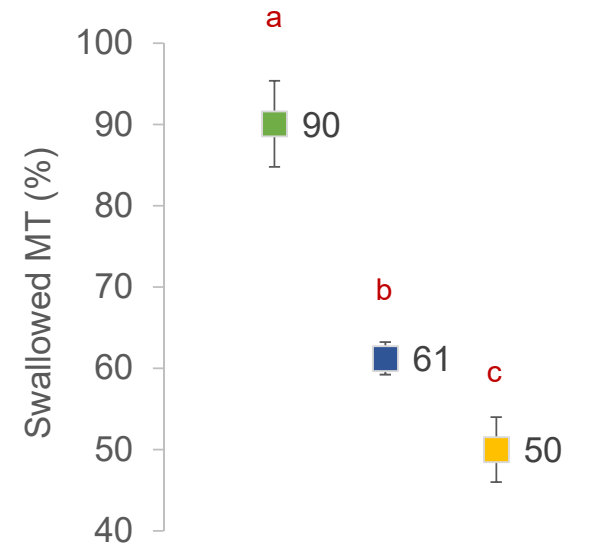
853

854

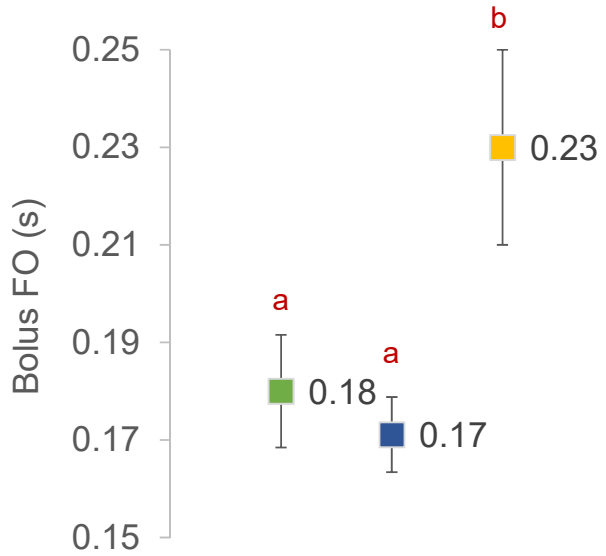
855

Figure 8

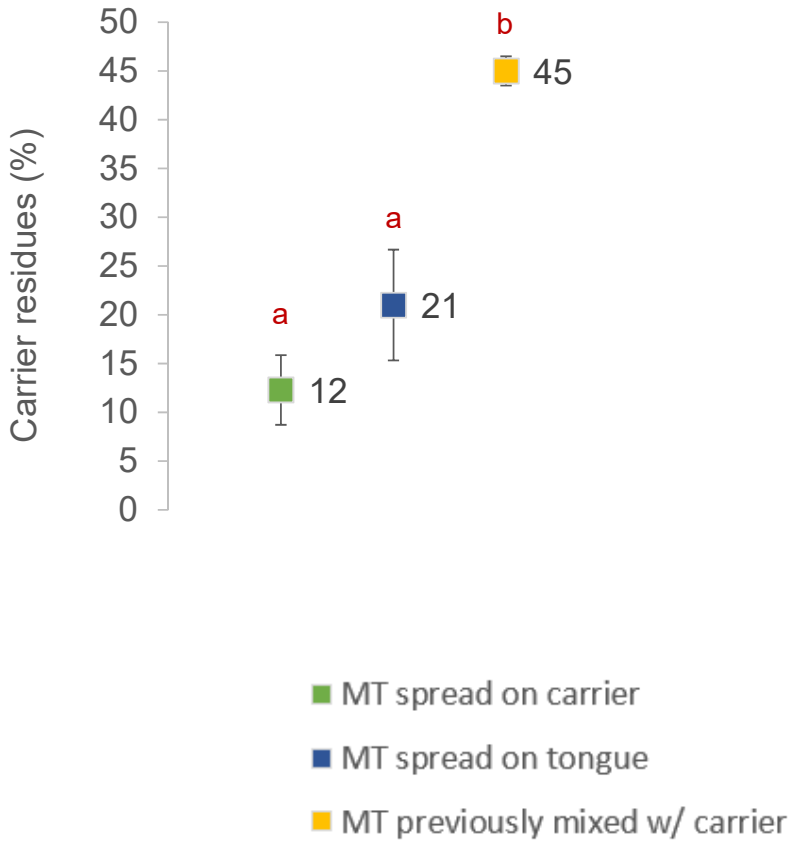
(a)


a
b
c
100
90
80
70
60
50
40
Swallowed MT (%)
90
61
50

(b)


b
a
a
0.25
0.23
0.21
0.19
0.17
0.15
Bolus FO (s)
0.23
0.18
0.17

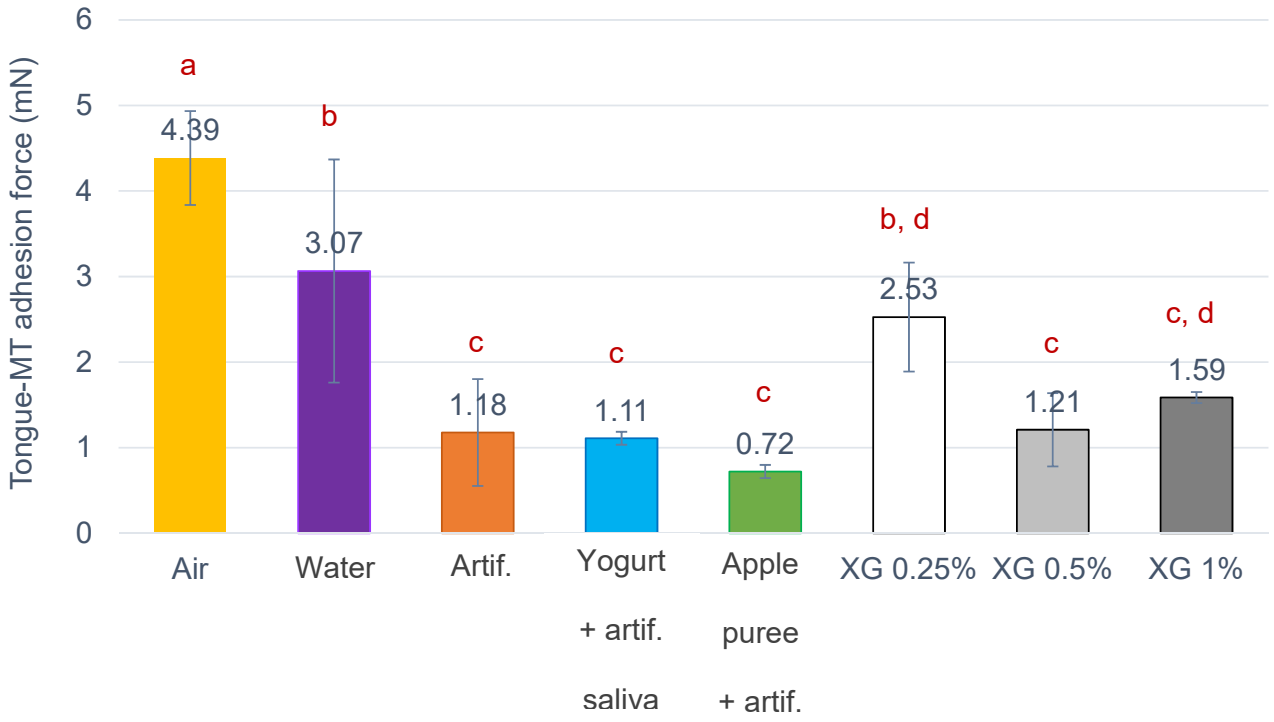
(c)


Carrier residues (%)
50
45
40
35
30
25
20
15
10
5
0
b
45
a
21
a
12
MT spread on carrier
MT spread on tongue
MT previously mixed w/ carrier

877 Figure 9

878

879



APPENDIX

Figure A: Maximal relative pressure values (kPa) measured in the oral cavity (mid-palate) with the different carriers.