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1 **Title**

2 **A novel soft robotic pediatric *in vitro* swallowing device to gain insights into the**
3 **swallowability of mini-tablets**

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16

17 **Keywords**

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

19

20 **Highlights**

21 • A novel soft robotic *in vitro* test inspired by the anatomy of a 2-year-old child was developed
22 based on data from the literature

23 • Based on the *in vitro* results, semi-solid foods like yoghurt and apple puree may be
24 considered more suitable than thin liquids for swallowing mini-tablets (MT).

25 • The reduction of MT size did not favour its *in vitro* swallowability in the range considered

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

30

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33 **ABSTRACT**

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

37 In this study a novel soft robotic *in vitro* device is presented, the Pediatric Soft Robotic Tongue
38 (PSRT), inspired by the literature data on the anatomy and physiology of a 2-year-old child.

39 Multi-particulate oral formulations (i.e., mini-tablets (MT)) were considered, including
40 different scenarios such as SODF carrier (i.e., soft-food, liquid), administration methods, SODF
41 size and volume fraction.

42 In vitro results showed that semi-solid foods like yoghurt and apple puree (shear viscosity above
43 ~ 150 mPa.s at $\dot{\gamma} = 50$ s⁻¹, and its yield stress up to ~ 5 Pa) may be considered more suitable
44 than thin liquids (i.e., xanthan gum 0.25%) for swallowing MT. However, the reduction of MT
45 size did not bring any benefit in terms of swallowability in the range studied. Regarding the
46 administration method, spreading MT on top of a teaspoon full of carrier should be preferred
47 over mixing MT with the carrier or placing MT on the tongue first to favour their
48 swallowability. Finally, and under the in vitro conditions studied using yoghurt as carrier, it
49 would be possible to increase the volume fraction of SODF up to 0.20 without influencing
50 swallowability according to the three parameters evaluated (% of MT swallowed, bolus
51 velocity, and post-swallow residues). These results should help to design more focused sensory
52 and/or clinical tests to improve product formulation and patient acceptability.

53

54 INTRODUCTION

55 Children need age-appropriate pharmaceutical formats, specifically designed, developed, and
56 evaluated for pediatric use (Mistry, Batchelor, and Uk 2017; Ternik et al. 2018). There,
57 acceptability is particularly important to achieve better clinical outcomes, as well as improving
58 the quality of life of young patients. According to the European Medicines Agency (EMA),
59 acceptability assessment must be included in the pediatric pharmaceutical development
60 program of new formulations and described in the pediatric investigation plan (Committee for
61 Medical Products for Human Use and Paediatric Committee 2013). However, knowledge in
62 this area is still limited, and different methodologies may be implemented due to uncertainties
63 of regulatory requirements as no international consensus has been established yet (Ternik et al.
64 2018).

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

71 Tablets and capsules are not recommended for children under 6 years old because of swallowing
72 difficulties and risk of choking. However, mini-tablets (≤ 4 mm in diameter), considered
73 suitable for children between 2 and 5 years (European Medicines Agency 2013; Mistry et al.
74 2017), are particularly interesting as they combine the stability of SODF with the dosage
75 flexibility of liquids (Mistry et al. 2017; van Riet-Nales et al. 2016). Several clinical studies
76 with placebos have shown that 2 years old children not only are able to swallow a mini-tablet
77 but was also preferred over alternative formulations like powders, suspensions, or syrups
78 (Klingmann et al. 2013, 2015; Musiime et al. 2014; Riet-Nales et al. 2013; Spomer et al. 2012;

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

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

97 Currently, the swallowability of multi-particulate formulations is evaluated during clinical
98 studies by direct observation of the child's mouth after administration ([Bracken et al. 2019](#);
99 [Klingmann et al. 2013, 2015, 2018](#); [Kluk et al. 2015](#); [Münch et al. 2021](#); [Spomer et al. 2012](#);
100 [Thomson et al. 2009](#)) or from parents reports about problems experienced during administration
101 at home ([Musiime et al. 2014](#); [Riet-Nales et al. 2013](#)). Nevertheless, pharmaceutical companies
102 need guidance to identify the key attributes that can improve swallowability before starting
103 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 *in 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).

129 MATERIALS & METHODS

130 1. Materials

131 1.1 *Carriers and insalivation ratio*

132 This study considered two food carriers, apple puree (“Pomme nature”, 100 g, Andros France
133 SNC, Biars-sur-Cère, France) and stirred yoghurt (“Velouté yaourt nature brassé”, 125 g,
134 Danone SA, Paris, France). Three different concentrations of xanthan gum (0.25, 0.5, and 1 %
135 w/v) in mineral water (Vittel) were also used (43708, xanthan from *Xanthomonas campestris*,
136 Sigma-Aldrich, St. Louis, MO, USA). Each food carrier was diluted with artificial saliva
137 (Brodkorb et al. 2019; Minekus et al. 2014) to mimic saliva incorporation during bolus
138 formation in the mouth before swallowing. In this study the artificial saliva did not contain α -
139 amylase. No information about saliva incorporation during bolus formation by toddlers was
140 found in the literature, but salivary flows seem to be similar between 2 years old and adults
141 (i.e., basal salivary flow rate (0.2-1 mL/min) and stimulated salivary flow rate (0.5-5 mL/min))
142 (Wollmer et al. 2022). Therefore, the amount of saliva incorporated when eating semi-solid
143 food products was estimated with adult volunteers, and calculated according to Drago et al.,
144 (2011). Briefly, five healthy volunteers (31 ± 10 years old) took a teaspoon of apple puree or
145 yoghurt, kept the product in mouth for 30 s, and spat it in a container. The ratio of saliva added
146 in the bolus with respect to the wet food sample (h_w) was 0.23 ± 0.10 , meaning that approx. 0.2
147 g of saliva were incorporated /g of semi-solid food. Based on these preliminary tests, the
148 dilution ratio (carrier: artificial saliva) was fixed at 5:1.

149 1.2 *Minitablets*

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

154 2. Rheological properties

155 The rheological properties of the carriers were assessed with a Modular Compact Rheometer
156 301 (Anton Paar GmbH, Graz, Austria) at 20°C. A concentric cylinder geometry (CC27) was
157 used to measure the properties of the apple puree and XG samples, and a parallel-plate system
158 (PP50, 1 mm gap) with a rough surface was used for yoghurt samples.

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

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

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

167 3.1 *Oral cavity*

168 The design of the oral cavity was adapted from a model of the oral airway constructed by [Xi](#)
169 [and Longest \(2007\)](#) based on CT scans of a healthy adult and measurements reported in the
170 literature. This model was modified to include the functionality of the tongue ([Marconati et al.](#)
171 [2020](#)). A smaller version of this 3D model was designed to stimulate the morphology of the
172 oral cavity at 24 months by selecting relevant anatomical features and measurements from
173 clinical studies on healthy children around this age reported in the literature ([Figure 1a](#)).

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

179 dentition of British children between 2 ½ and 3 years old. Finally, the values extracted by
180 [Vorperian \(2005\)](#) from observations by MRI of the hard and soft tissue vocal tract structures of
181 2 years old children in Wisconsin (USA), and particularly the hard and soft palate lengths, were
182 considered as a representative measure of the arc length of the oral cavity (ie., 66 mm).
183 The top of the oral cavity was pierced with 4 holes located at 1, 5.8, 22.8 and 44.8 mm from the
184 tongue tip along the sagittal direction. Two large holes with 1/8” metallic nuts glued on top
185 were used to tightly screw pressure transducers to record the dynamic evolution of palatal
186 pressure during swallowing tests of liquid samples. The last two were used as feeding holes: a
187 large one (14 mm diameter) to feed small solids like mini-tablets or foods containing large
188 particles (hermetically sealed with a rubber stopper during the swallowing tests), and a small
189 one (4 mm diameter) where a plastic tube was fitted and used to feed liquids from a syringe
190 pump. The oral cavity was 3D printed in a transparent material (VeroClear® resin) to allow
191 bolus movement observation during swallowing.

192 3.2 Soft robotic tongue

193 A soft actuator was designed by [Marconati et al., \(2020\)](#) to reproduce the peristaltic movement
194 of the tongue. This soft robotic tongue was made up of two air chambers that can be inflated
195 and deflated independently to reproduce key lingual functions: bolus containment prior to
196 swallowing, and bolus propulsion during the oral phase of swallowing. The shape obtained
197 during a swallowing test has been compared qualitatively against *in vivo* ultrasound imaging of
198 the tongue ([Mowlavi et al. 2016](#)). The tongue was produced by casting silicone rubber (Smooth-
199 On Eco-flex 00-30) mixed with 0.5% w/w of a nonionic surfactant (sorbitan mono-oleate, Span
200 80, CAS: 1338-43-8, from Sigma Aldrich) in a mold. Mechanical properties and wettability
201 were similar to the human tongue ([Marconati et al. 2020](#)). This soft actuator was adapted to
202 mimic the tongue of a 2-year-old child by scaling down the adult model to obtain a pediatric

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

205 3.3 Swallowing pattern

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

219 3.4 In vitro swallowing conditions

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

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

229 3.5 Measured variables

230 *Swallowed MT (%)*

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

234 *Bolus velocity (s)*

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

239 *Carrier residues (%)*

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

$$243 \quad m_{residues} = m_{sample\ fed} - m_{sample\ swallowed} \quad (1)$$

$$244 \quad m_{carrier\ residues} = m_{total\ residues} - m_{particles\ left\ in\ the\ cavity} \quad (2)$$

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

246 *Palatal pressure (kPa)*

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

252 4. Adhesion measurements

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

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

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

267 5. Statistical analysis

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

272

273 RESULTS AND DISCUSSION

274 1. Rheological properties of the carriers

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

279 In adults, the shear rates ($\dot{\gamma}$) during human swallowing have been estimated to be in a range
280 between 1 s^{-1} in the mouth, and up to 1000 s^{-1} in the pharynx (Gallegos et al. 2012; Nishinari et
281 al. 2016). The shear rheology of texture modifiers and food products is commonly reported at
282 $\dot{\gamma} = 50 \text{ s}^{-1}$. Oral shear rates for 2-year-old are unknown, and there is no consensus on the shear
283 rates most representative of food oral processing in infants and young children (Makame, De
284 Kock, and Emmambux 2020; Steele et al. 2015; Sukkar et al. 2018).

285 All the samples showed a shear thinning behaviour (i.e., viscosity decreased rapidly with
286 increasing shear rate) in the whole range of shear rates studied ($1 - 500 \text{ s}^{-1}$). The XG suspensions
287 had a more pronounced shear thinning behavior than the food carriers. The apple puree diluted
288 with artificial saliva and XG 1 % had similar shear viscosities at $\dot{\gamma} = 50 \text{ s}^{-1}$ (587 ± 14 and 460
289 $\pm 59 \text{ mPa.s}$, respectively); the yoghurt diluted with artificial saliva and XG 0.5 % had similar
290 shear viscosities at $\dot{\gamma} = 50 \text{ s}^{-1}$ (209 ± 5 and $167 \pm 1 \text{ mPa.s}$, respectively). Compared to Newtonian
291 fluids like syrups, shear thinning fluids require less efforts in oral processing and swallowing
292 (Steele et al. 2015) but could also be less effective in “masking” the presence of particles in the
293 mouth as their viscosity decreases under the relatively high shear rates experiences during oral
294 processing (Steele et al. 2015).

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

298 effort needed to swallow a bolus: when τ_0 increases the tongue force necessary to make the
299 carrier flow will also increase (Cichero and Lam 2014; Malouh et al. 2020). The XG suspension
300 1 % had the highest estimated τ_0 (12.2 ± 0.9 Pa) and XG 0.25 % the lowest (0.9 ± 0.2 Pa).
301 Intermediate τ_0 were found for XG 0.5 % and the food carriers diluted with artificial saliva
302 (between 2 and 5 Pa).

303 2. Mini-tablets swallowability *in vitro*

304 2.1 Effect of the type of semi-solid carrier on mini-tablets swallowability *in vitro*

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

310 Overall, high success rates were reached with more than 75 % of the MT successfully
311 swallowed (Fig. 4a) but differences were observed depending on the rheological properties of
312 the carriers. A lower number of MT were swallowed with XG 0.25 % in these conditions ($77 \pm$
313 7 %). This carrier had a low shear viscosity (ca. 60 mPa.s at $\dot{\gamma} = 50$ s⁻¹), and a low yield stress
314 (0.9 Pa). Consequently, MT were able to sediment in the bolus during the initial part of the test
315 and were positioned on the tongue when the swallow was triggered (Fig. 5c). Interactions
316 between the artificial tongue and MT, such as adhesion, may affect the swallow of the particles.
317 Moreover, it has been shown *in vitro* that low viscosity fluids are not the most efficient carriers
318 for SODF as they tend to flow faster than the particles which lag behind the liquid bolus
319 (Lavoisier et al. 2021; Marconati et al. 2018).

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

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

324 When swallowed with XG 1 % and the apple puree diluted with artificial saliva, very high
325 success rates were also reached ($\geq 90\%$). In this case, the shear viscosity of the carriers was
326 too high for the MT to sediment in the bolus (η between 460 and 590 mPa.s at $\dot{\gamma} = 50\text{ s}^{-1}$) (Fig.
327 5e). Interestingly, the apple puree gave better results than XG 1% ($96 \pm 2\%$ against $90 \pm 2\%$,
328 respectively), which may be caused by the XG 1% high yield stress (4.5 for the apple puree vs.
329 12.2 for XG 1 %) or the slightly higher viscosity of apple puree at shear rates above 100 s^{-1} .

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

339 Bolus velocity and post-swallow residues were not influenced by the type of carrier used. Bolus
340 FO was measured between 0.16 and 0.19 s (Fig. 4b) which is coherent with the physiological
341 duration of the oral phase of swallowing (i.e., $< 0.5\text{ s}$) (Almeida et al. 2008; Frakking et al.
342 2017; Rommel et al. 2006, 2014). Carrier post-swallow residues were low, between 5 and 10
343 % of the initial amount of carrier fed (Fig. 4c), which indicates that all sample boluses were
344 effectively transported and ejected during the swallowing tests. Finally, the maximum relative
345 pressures in the oral cavity were measured mid-palate between 8 and 10 kPa and were not
346 influenced by the type of carrier used (Appendix Fig. A).

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

354 2.2 Effect of the size of the mini-tablets on their swallowability in vitro

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

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

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

372 *2.3 Effect of the particle volume fraction on mini-tablets swallowability in vitro*

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

378

379 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

380

381

382 As expected, increasing the volume fraction of MT (and the total volume of bolus swallowed)
383 resulted in a decrease in the percentage of MT successfully swallowed, and in an increase of
384 post-swallow residues (FIG. 7a and 7c, respectively). From 0.05 to 0.20 particle volume
385 fraction, a very high success rate was observed ($\geq 90\%$), whilst bolus velocity was not impacted
386 (bolus FO between 0.18 and 0.20 s) and post-swallow residues were low ($\leq 15\%$). 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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727

728 **Figures captions :**

729

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

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

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

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

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

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

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

747 **Figure 8:** (a) % of MT swallowed, (b) bolus velocity (s), (c) % of carrier residues
748 depending on the administration method. Red letters indicate significant differences (p
749 < 0.05).

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

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756

757 Figure 1

758 (a)

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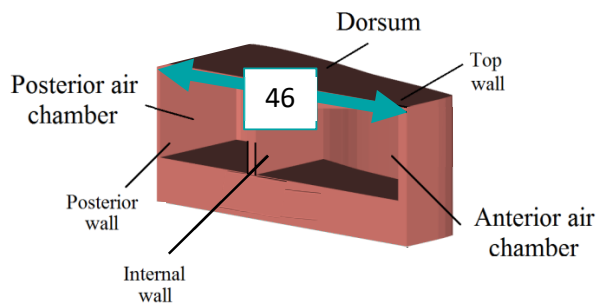
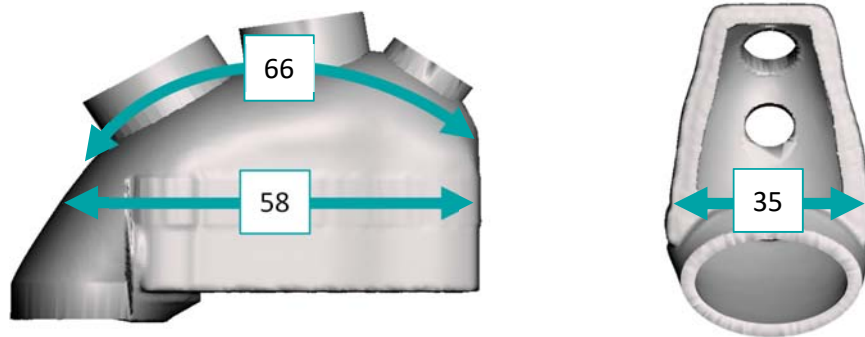
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776 (b)

777



778 Figure 2

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780

781

Compression

Return to initial

782

to F_{max}

783

Compression probe

$F_{Adhesion}$

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785

786

Mini-tablet

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Artificial tongue

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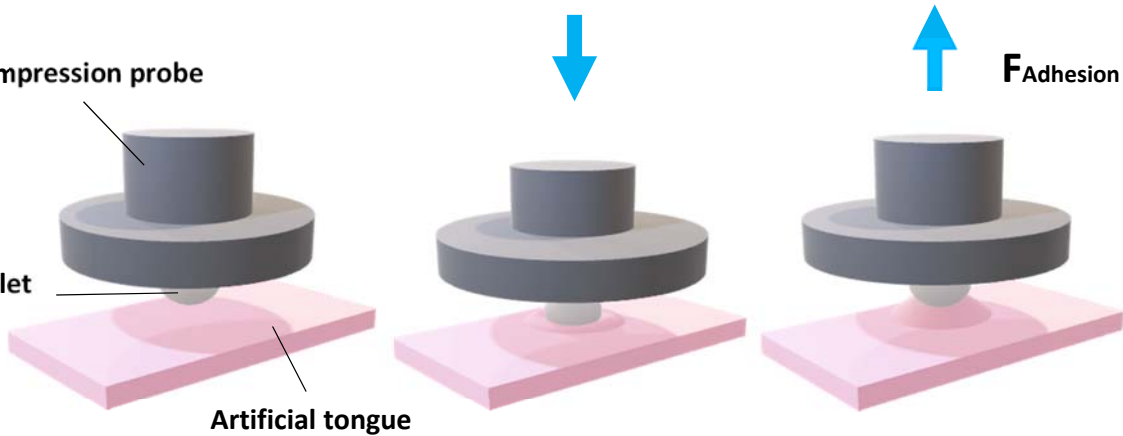
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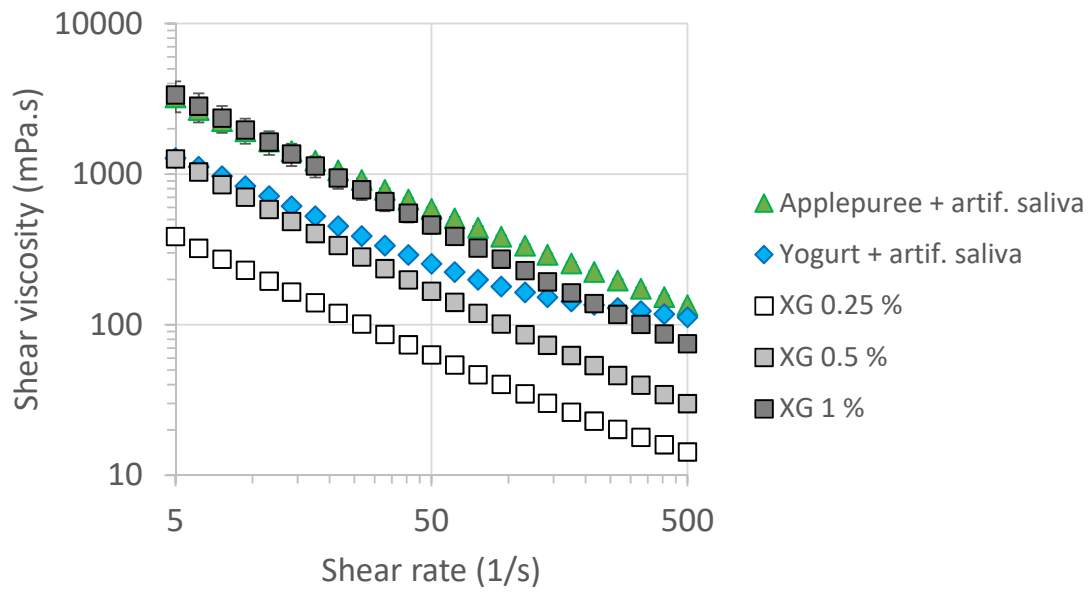
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794 Figure 3

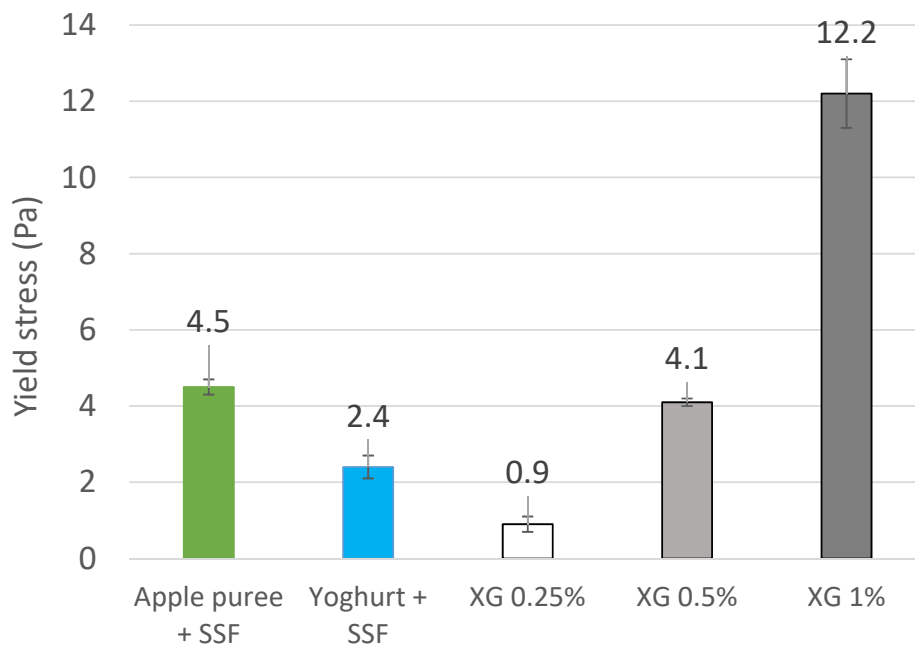
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796 (a)



797

798 (b)

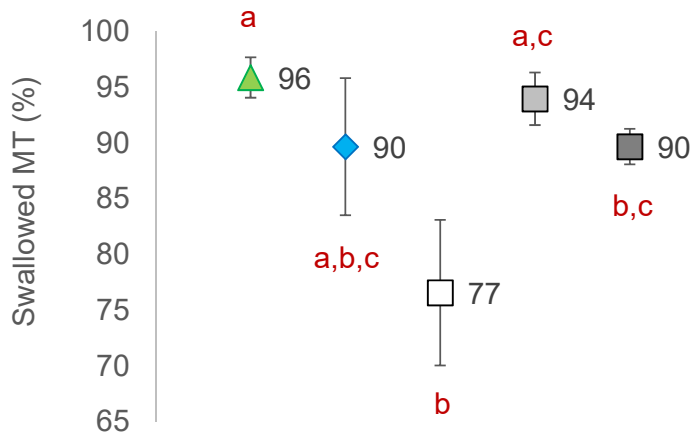


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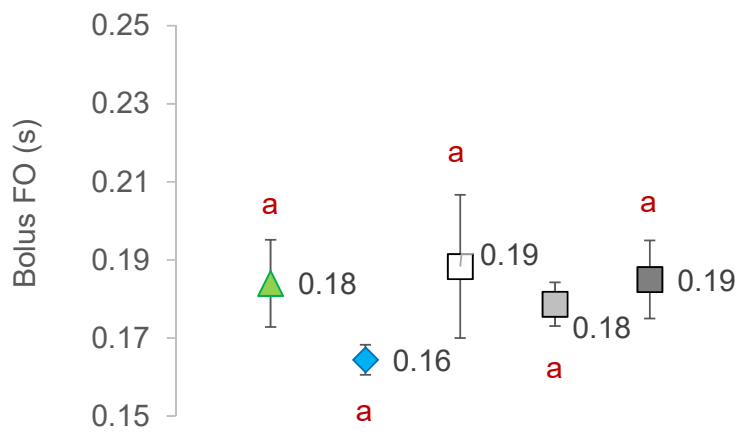
801 Figure 4

802 (a)



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804 (b)



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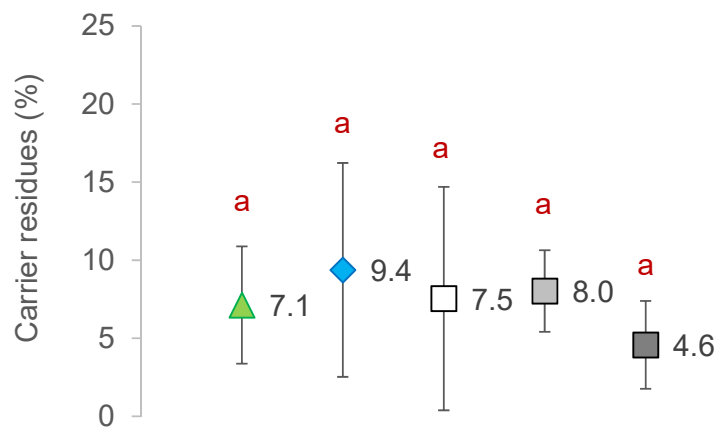
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814 (c)

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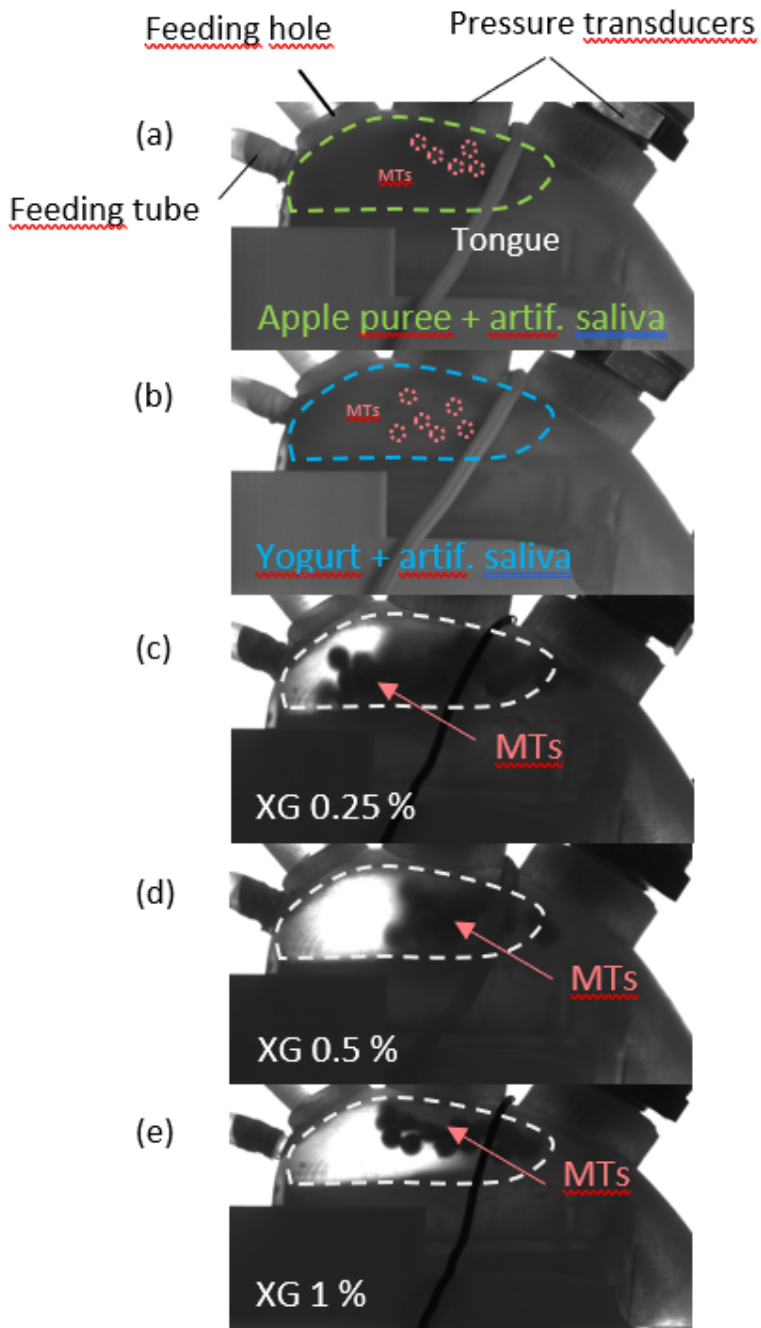


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▲ Apple puree (+SSF) ◆ Yogurt (+SSF) □ XG 0.25 % ■ XG 0.5 % ■ XG 1 %

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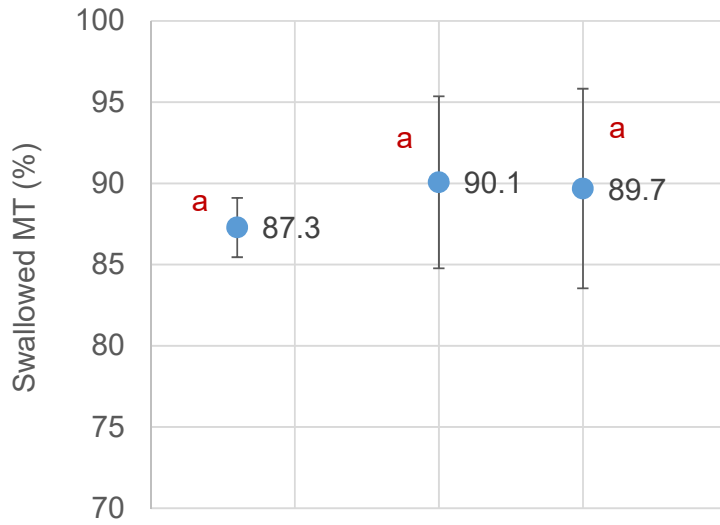
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822 Figure 6

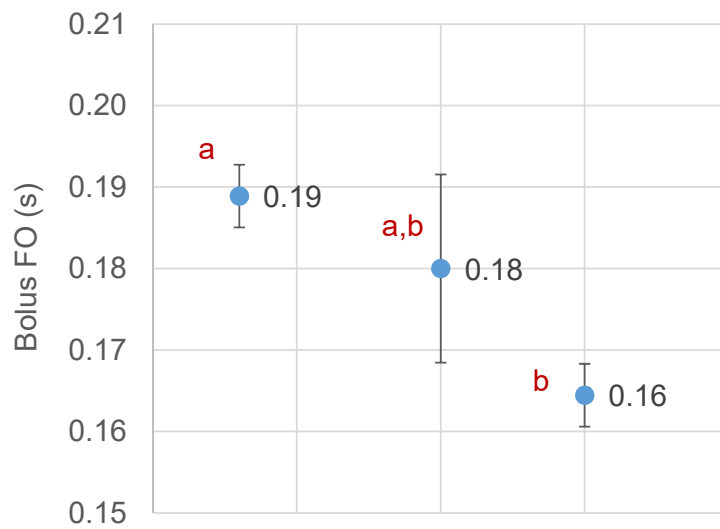
823

824 (a)



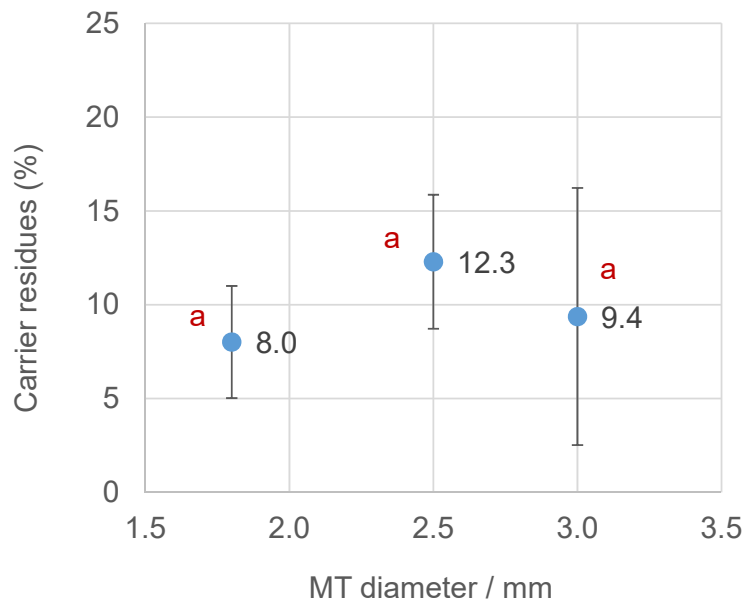
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826 (b)



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828 (c)



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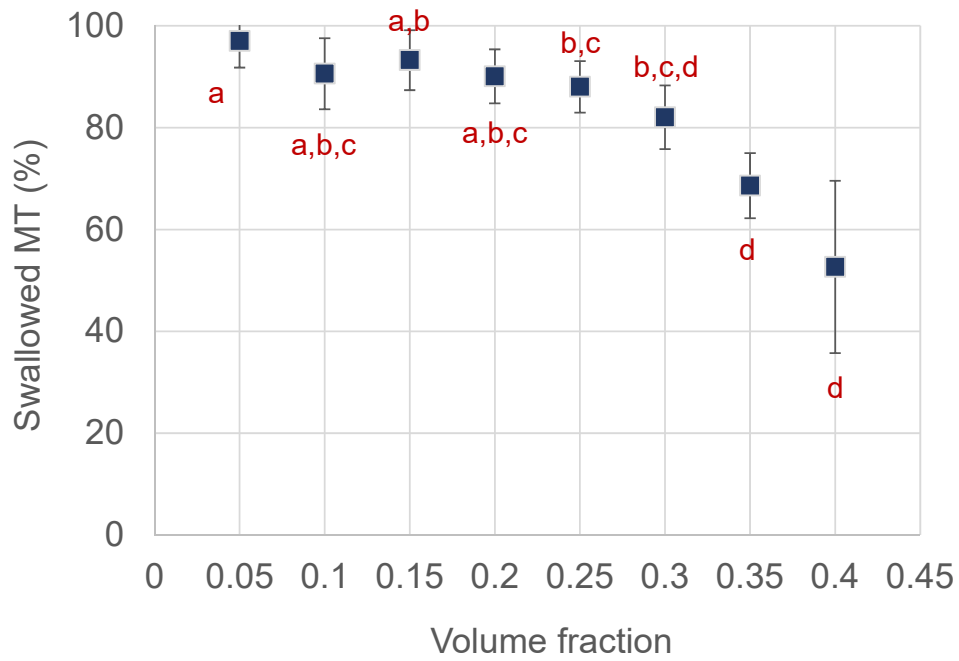
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834 Figure 7

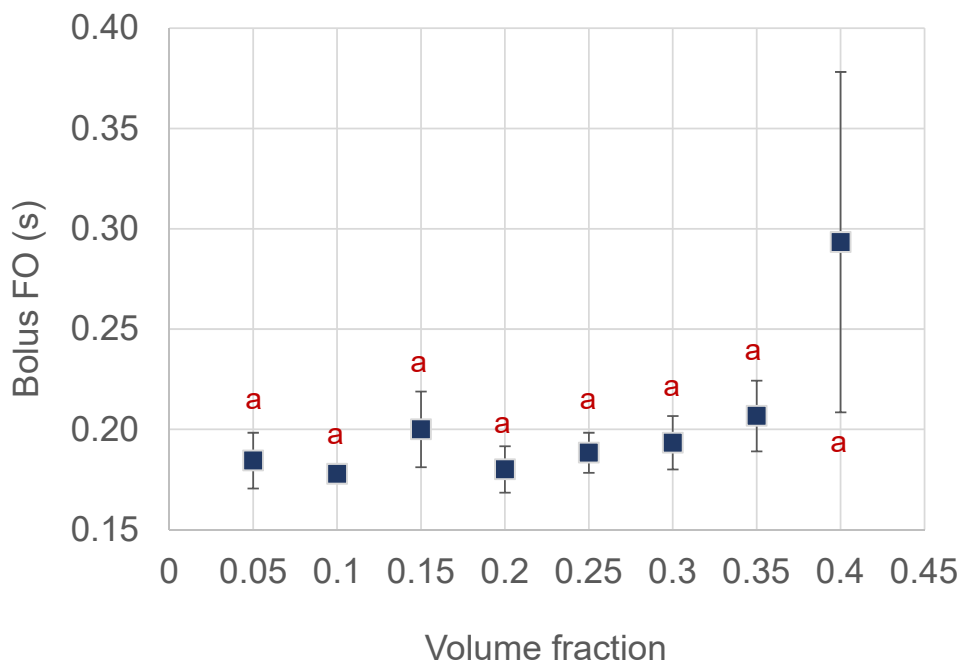
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836 (a)



837

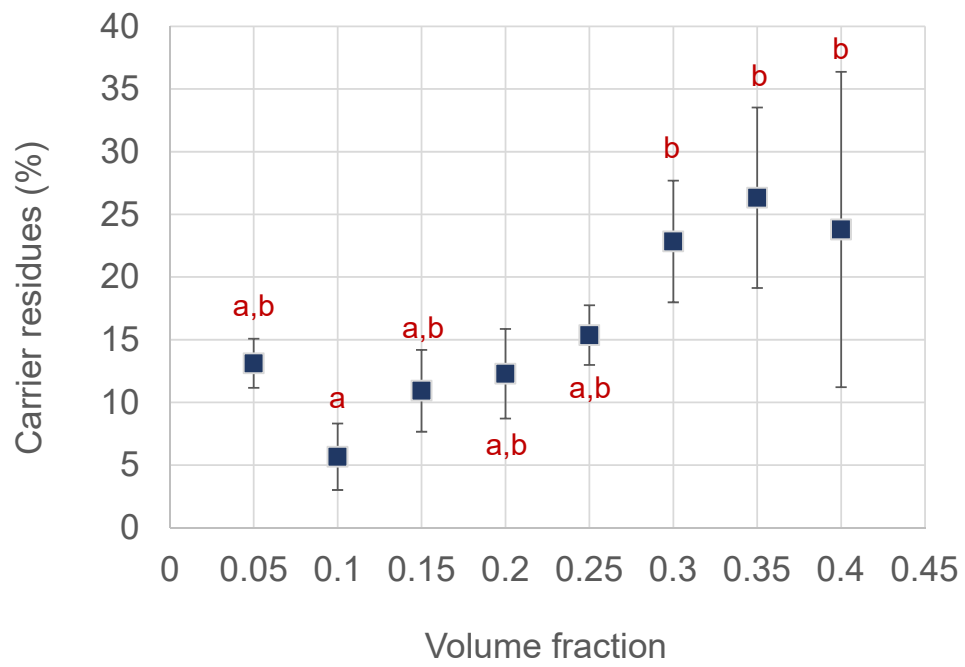
838 (b)



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841 (c)



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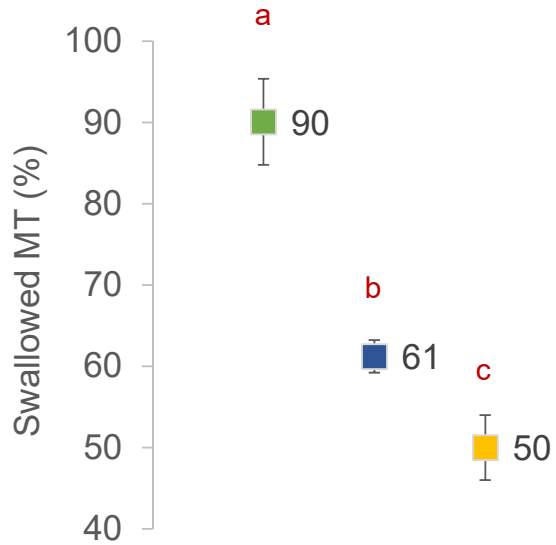
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856 Figure 8

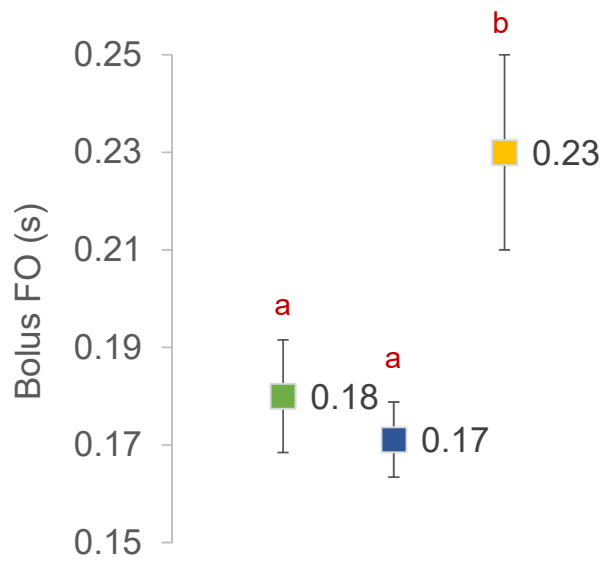
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858 (a)



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860 (b)



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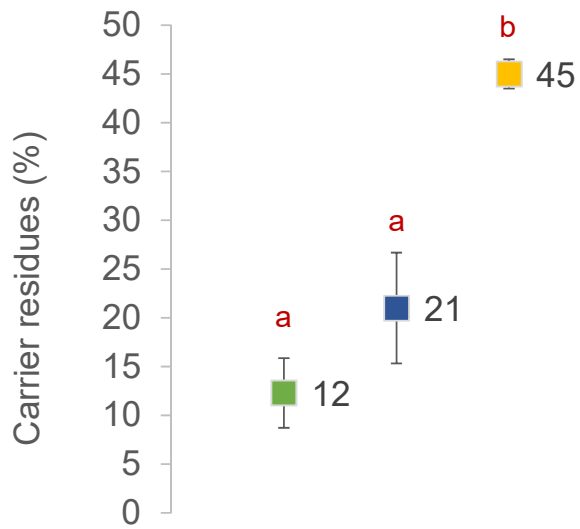
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868 (c)



869

870

871

■ MT spread on carrier

872

■ MT spread on tongue

873

■ MT previously mixed w/ carrier

874

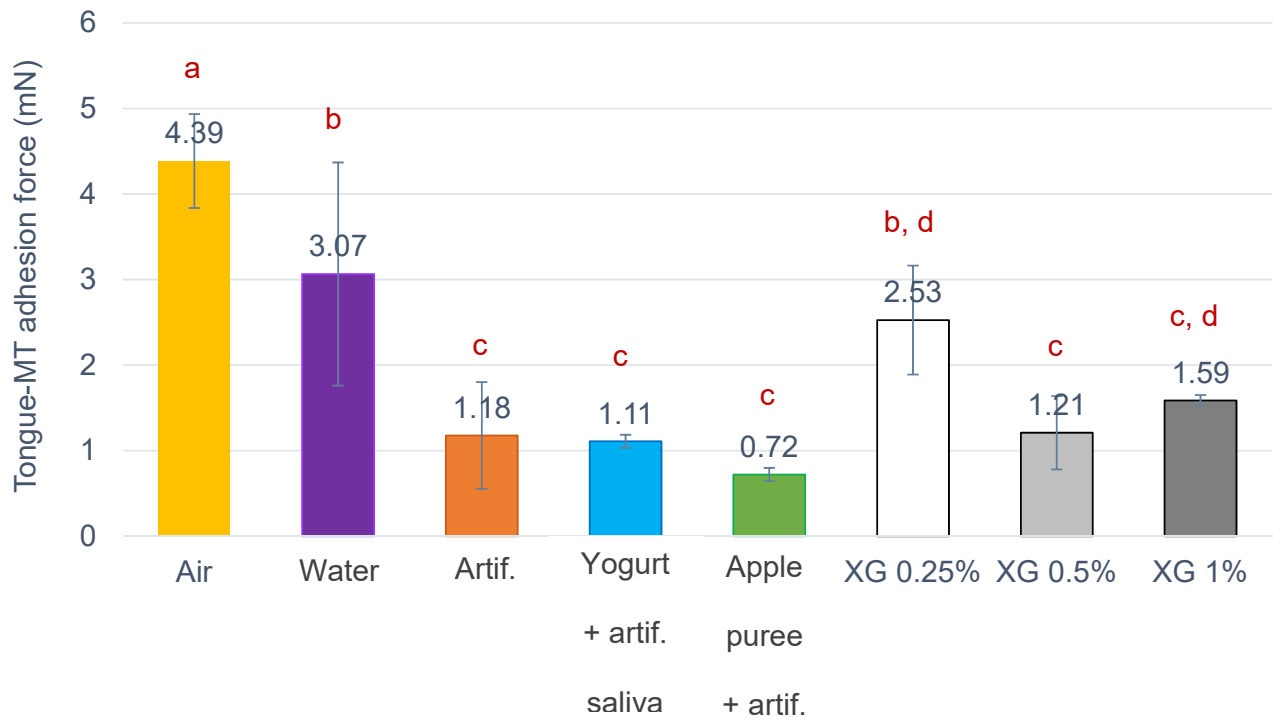
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877 Figure 9

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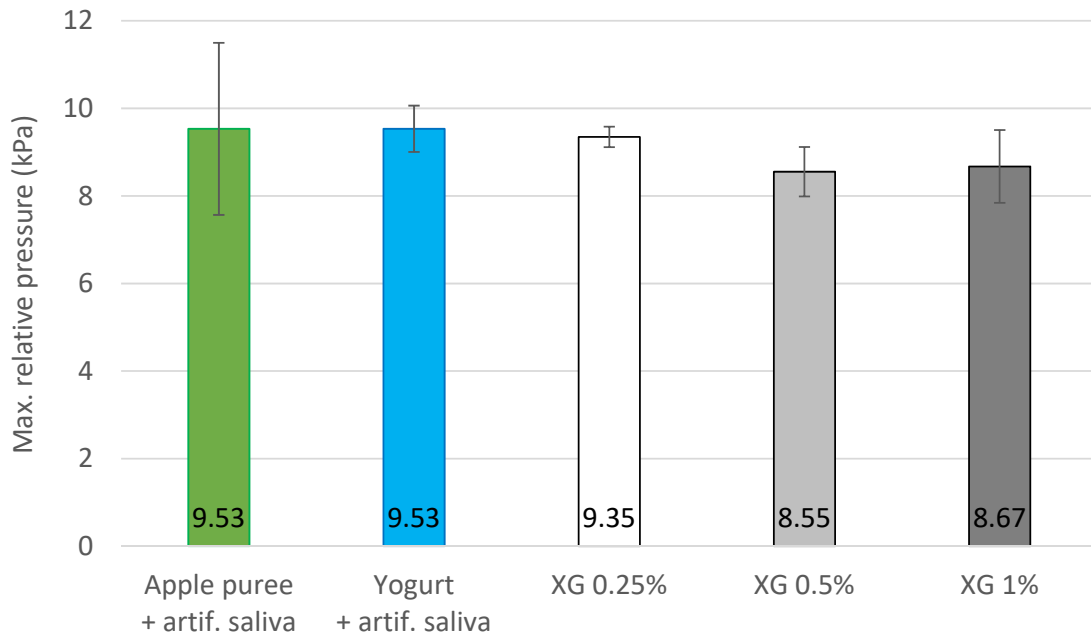


880 **APPENDIX**

881

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

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