

1 **The application of tribology in assessing texture perception of oral liquid medicines.**

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20 **Abstract**

21 The palatability of medicines is likely to have a significant impact on patient adherence and
22 consequently, on the safety and efficacy of a medicinal product. Palatability encompasses
23 properties of medicines not limited to taste including swallowability (e.g. size, shape,

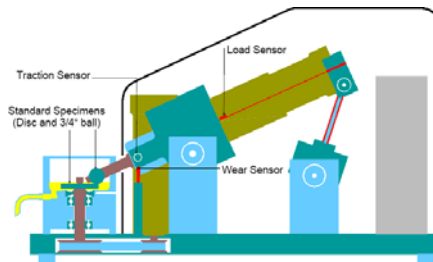
24 texture). However, there has been limited work undertaken to measure the texture of
25 medicines and how this may affect palatability and subsequent adherence.

26 Tribology offers an understanding of oral processes and can allow physical properties of
27 materials to be linked to “mouthfeel”. This paper describes a preliminary application of
28 tribology to oral liquid medicines and demonstrates that this technique is useful in the
29 development of future oral liquid medicines.

30 **Keywords: Tribology, texture, mouthfeel, medicine,**

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32 **Graphical abstract**



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Medicine → Tribology → acceptability

36 1 Introduction

37 Patient acceptability is likely to have a significant effect on medicines adherence and
38 consequently on the safety and efficacy of the medicinal product. Recent EMA guidelines
39 have highlighted that the palatability of a medicine is one of the main elements of patient
40 acceptability of an oral paediatric medicinal product (EMA, 2013). Palatability is defined as
41 the overall appreciation of a medicinal product in relation to its smell, taste, aftertaste and
42 texture (i.e. feeling in the mouth). It is determined by the characteristics of the active
43 substance, the way the active substance is formulated into a finished medicinal product and
44 by the characteristics of the excipients.

45 Much work has been done on the assessment of taste of medicines (e.g. (Baguley et al.,
46 2012; Rieder, 2012; Smith et al., 2013; Somasiri et al., 2013)) but there are very limited
47 reports on the influence of texture of medicines. Allué et al (2012) evaluated the organoleptic
48 properties of oral rehydration solutions in children, including the influence of texture by
49 comparing a “gelatine” and “gel” texture; their results showed that the “gel” texture was
50 preferred however, no further details on this finding were provided (Polanco Allué et al.,
51 2012). The need to improve the texture of medicines was also highlighted for antiretroviral
52 therapies (2004; Gibb et al., 2003), although details on textural issues were not explicitly
53 reported. The texture of nelfinavir powder has been reported to be an issue in terms of
54 palatability of medicines (Reddington et al., 2000; Van Dyke et al., 2002). Nelfinavir is
55 administered in large volumes, for instance, at the dose of 55 mg/kg BID, an average 6-year-
56 old is required to take 25 scoops (6.25 teaspoons) of nelfinavir powder, with food, twice a
57 day.

58 A recent study investigated barriers to medicines administration in children and although
59 taste was the most reported issue in medicines refusal texture was the next most frequent
60 reason for refusal (Venables et al., 2014). Specific medicines identified with textural issues
61 included: lactulose which was described as “oily” and co-trimoxazole liquid described as
62 “thick and gelatinous” (Venables, 2014).

63 There are no reports on the ideal mouthfeel of a liquid medicine; however it is intuitive to
64 suggest that this needs to be smooth and in the case of a bad tasting medicine a product
65 that is swallowed rapidly and leaves minimal residue on the oral cavity surfaces. Positive
66 attributes of oral formulations reported in a recent study described good textures as being
67 “sherbet” and “fizzy” (Venables, 2014).

68 The mouthfeel of a medicine can be defined as the sensation from the ingestion, mastication
69 and swallowing of the medicine, all of which are influenced by the physical and chemical
70 properties of the medicine being administered. The majority of mouthfeel research has been
71 conducted on foods where there is a tendency to want to maximise sensory pleasure in food
72 consumption to drive preferences in food choices, however, there are key differences
73 required in assessing the mouthfeel of medicines. Medicines are designed to be acceptable
74 rather than preferred choices and there is no requirement to maximise sensory pleasure.
75 Nevertheless, it is critical that the mouthfeel of a medicine is not a barrier to administration.

76 Orally administered medicines are manipulated by the tongue, teeth, inside of the cheeks
77 and lips whilst in the oral cavity; this subjects the medicine to forces at a range of speeds
78 and pressures (Prinz et al., 2007). There are various sensory textural attributes that patients
79 perceive whilst taking oral medicines (as with foods) including hardness, softness, grittiness,
80 creaminess, adhesiveness, slipperiness and many others (De Wijk and Prinz, 2006).

81 Research in food science has attempted to qualify and quantify physical properties of foods
82 and link *in vitro* measurements to sensory attributes. For example, rheological properties
83 have been linked to thickness and breaking forces linked to crispiness (Koliandris et al.,
84 2010; van Vliet et al., 2009). Tribology is considered the most appropriate method to
85 measure phenomena related to attributes such as creaminess, slipperiness and coating of a
86 liquid on oral surfaces as these are sensations associated with rubbing and squeezing
87 actions within the mouth. Tribology is the study of thin film lubrication (Prakash et al., 2013).

88 The use of tribology for the study of friction and the behaviour of foods is a relatively new
89 application of this measurement system which has been shown to differentiate foods on the

90 basis of their creaminess (Chojnicka-Paszun et al., 2012; Dresselhuis et al., 2008; Sonne et
91 al., 2014) and other textural parameters (Mills and Norton, 2013). In general, it is accepted
92 that while tribology does not provide a one-to-one relation to processing in the mouth, when
93 combined with a number of other characterisation techniques such as rheology, it can offer
94 valuable information on material behaviour. This knowledge can then be used to help guide
95 the design of new products. This paper describes the first use of tribology to assess the
96 lubricating properties of oral liquids.

97 In brief, tribology measures the friction between two interacting surfaces, in this case a steel
98 ball on a silicone elastomer disk. Lubrication is often categorised by measuring the friction
99 coefficient across a range of speeds as the extent of lubrication will vary. Often this data is
100 presented as a Stribeck curve, which shows the traction coefficient as a function of speed of
101 motion between surfaces. The Stribeck curve usually has three phases:

- 102 1. Boundary regime: where the speed is low, this measures the ability of the fluid to wet
103 or adsorb to the surface and has in some cases been linked to astringency/grittiness
104 (Rossetti et al., 2009)(high value of friction) and slipperiness/oiliness (low value of
105 friction)(Malone et al., 2003; Prakash et al., 2013).
- 106 2. Mixed regime: where the speed is intermediate and the fluid present can partly
107 separate the two rubbing surfaces. The friction coefficient reaches a minimum in this
108 regime and typically lower values have been associated with creamy textures
109 (Chojnicka-Paszun et al., 2012).
- 110 3. Hydrodynamic regime: where the speed is high and the fluid separates the surfaces;
111 the film thickness and friction generated are dependent upon the viscosity of the
112 food. Often rheology provides greater insights at these speeds to characterise the
113 fluid present.

114 In terms of application of tribology to liquid medicines in the mouth we are mostly interested
115 in low to intermediate speed movement (boundary/mixed regime as described above) to

116 assess the ability of a medicine to coat the oral cavity as we hypothesise that a low-residue
117 (non-coating) product is likely to be preferred and it is these regions that have previously
118 been identified to be most relevant when considering oral processing (Malone et al., 2003).

119 Many oral liquid medicines are formulated as suspensions where drug particles are
120 undissolved within the bulk liquid. The size of the drug particles will influence their mouthfeel
121 as they may result in a gritty texture. Previous work conducted reported that particles as
122 small as 2 μm could be detected in food by trained adult panels (Engelen et al., 2005a).
123 However, the perception of size of particles was influenced by their characteristics where
124 hard and irregular particles are perceived as larger than soft and round particles of similar
125 size (Engelen et al., 2005b).

126 The objective of the present study is to evaluate the effectiveness of tribology as a tool to
127 differentiate between oral liquid medicines based on qualitative feedback regarding their
128 texture. The frictional response of each liquid is measured over a range of speeds to map
129 the Stribeck response for each product and compared with viscosity to emphasise the
130 different information that can be gained from this method. We highlight the potential of
131 tribological measurement to provide insights into texture and mouthfeel perception of
132 medicines.

133 **2 Materials and methods**

134 2.1 Medicinal products

135 Oral liquid medicines were selected based on qualitative data from previous work where co-
136 trimoxazole (Septrin®) and Lactulose were reported as having thick and oily textures
137 respectively (Venables, 2014). Calpol® infant sugar free 120mg/5mL suspension is typically
138 reported to be an ideal medicine in terms of palatability and therefore this was used as a
139 control. Other generic paracetamol suspensions were investigated to observe whether
140 tribology could differentiate between brands.

141 Septrin® Paediatric suspension 40mg/200mg per 5mL (Aspen); Septrin® adult suspension
142 80mg/400mg per 5mL (Aspen); generic paracetamol sugar free oral suspension 120mg per
143 5mL (Edict); Calpol® paracetamol sugar free oral suspension 120mg per 5mL (McNeil);
144 generic paracetamol sugar free oral suspension 250mg per 5mL (Pinewood laboratories);
145 lactulose (TEVA UK) were sourced from a local pharmacy (Queen Elizabeth Hospital
146 Pharmacy) and used as received.

147 2.2 Tribology apparatus and measurement

148 The friction properties were measured using a mini traction machine (MTM2 PCS
149 Instruments, London). The machine consists of a 19.05 mm steel ball loaded onto a 46mm
150 diameter silicone elastomer disc, which are independently driven to allow different relative
151 motion. Temperature was controlled at 20 °C. Typically medicines are retained in the mouth
152 for <20 seconds therefore 20 °C is more representative of the temperature of the product
153 compared to body temperature (37 °C). Stribeck curves were formed for all samples by
154 measuring traction from 1-1500 mm/s with a 2 N normal force. 2 N was chosen to provide
155 contact pressures relevant to oral processing (order of magnitude) found from literature (Hori
156 et al., 2009) while maintaining repeatable data as established in previous work by the
157 authors (Mills et al., 2013). Each sample was measured six times alternating from ascending
158 and descending speeds to check for hysteresis. Hysteresis can sometimes occur when
159 samples are physically altered by the shear in the testing process itself, if this is the case
160 subsequent speed sweeps could drift in value and using an average would not be
161 appropriate when presenting the final results, this was not evident in the measurements
162 reported here. Measurements were performed in triplicate and are presented as an average
163 with error bars of one standard deviation.

164 2.3 Rheological measurement

165 Bulk rheology of the products was measured to act as a comparison to the tribology data
166 obtained. A Bohlin Gemini HR nano rheometer (Malvern, UK) was used; fitted with a 20 mm

167 4° cone and plate at 20 °C. Shear rates from 0.01 to 300 s⁻¹ ascending and descending
168 were applied. Results are presented as an average of three repeats with error bars of one
169 standard deviation.

170 2.4 Particle size and shape

171 A drop of each commercial product was placed onto a microscope slide and a coverslip was
172 used to prevent dehydration of the sample. A Zeiss Axiosop 2 Plus upright microscope was
173 used to view each product to directly observe the particle size and shape at x10
174 magnification. The axiovision programme was used to capture a representative image from
175 each sample together with a scale bar. The crystals were measured at their widest part in
176 two perpendicular directions from 3 fields of view where at least 4 crystals were present (a
177 total of n=12 crystals were included) and the mean diameter reported together with one
178 standard deviation for each product. Analysis of Variance (ANOVA) tests were performed at
179 a significance level of 5%. Results were stated to be different when the p value was less
180 than 0.05.

181 **3 Results and discussion**

182 3.1 Tribology and rheology

183 The lubricating properties of the medicines were measured to determine if any differences
184 could be identified for a range of samples. An overall comparison of the five samples is
185 made as well as two smaller comparisons within the Seprin formulations and the
186 paracetamol formulations. Figure 1 shows the Stribeck curves collected where the traction
187 coefficient is plotted as a function of speed for all samples. Under the conditions studied,
188 differences in the materials can be observed mainly at low to intermediate speeds. These
189 differences relate to the lubricating properties and entrainment between the measurement
190 surfaces of the materials and would highlight differences that could be perceived during
191 consumption. The oily nature of lactulose as identified in earlier work is evident from the low

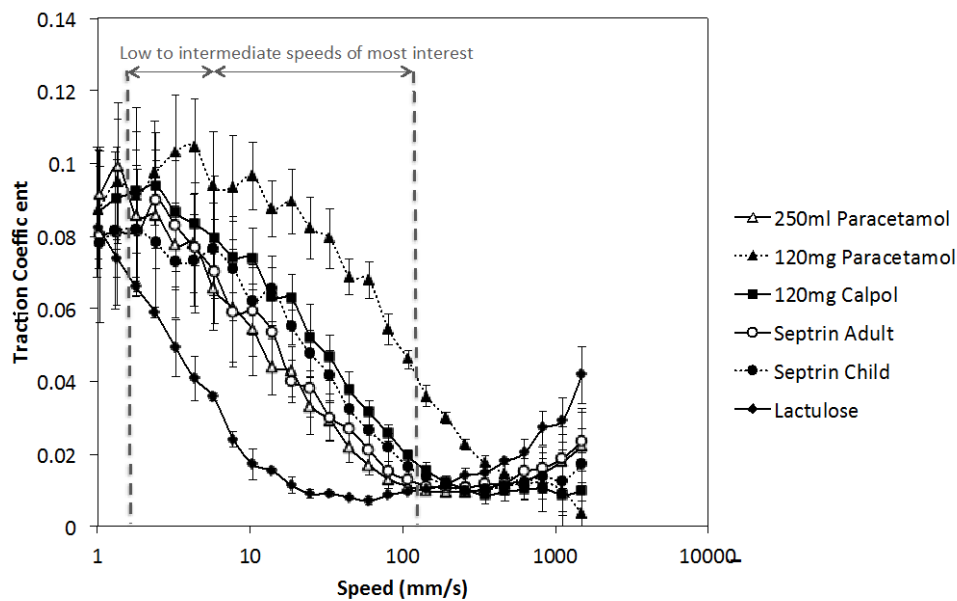
192 traction coefficient values, which demonstrates that this product is likely to coat surfaces
193 easily.

194 Gritty or “dry” products are anticipated to show high traction coefficients at low speeds due to
195 their lack of lubrication and surface coating. Many liquid medicines are suspensions with
196 particle sizes ranging from 1 to 50 μm (Allen et al., 2005). However, there is currently no
197 data that correlates grittiness perception in medicines to particle size. This study used
198 products with particle sizes that are known to be detectable in human panel studies which
199 also represent typical liquid medicines. The fact that Calpol® does not result in higher friction
200 values or a gritty mouthfeel despite having particles large enough to be perceived could
201 suggest that, as suggested by Engelen *et al.*, the particles are not hard enough to affect
202 perception or that their shape is affecting their perception (Engelen et al., 2005a). For the
203 generic paracetamol samples a large difference is identified between the different brands
204 with the 250 mg/5mL product being more lubricating overall and very similar to the Calpol®
205 formulation. When compared to viscosity (see Figure 2) at lower shear rates both generic
206 products behave similarly to each other, with the Calpol® at a reduced viscosity at lower
207 shear rates, however the 120 mg/5mL product is more shear thinning (i.e. viscosity reduces
208 with increasing shear rate) which would suggest a reduced ability to support the contacting
209 surfaces and reduce lubrication for the tribology measurement. These differences are
210 expected since the different brands would use different formulations but these changes in
211 behaviour highlight why two products may have very different feedback on their palatability
212 despite containing the same quantity of active ingredient.

213 Both Septrin® formulations show very similar lubrication behaviour and viscosity over the
214 studied range, which could be expected since they are both from the same manufacturer.
215 Despite having different concentrations of active ingredient these results suggest that the
216 excipients likely dominate the material behaviour, so any differences experienced in liking
217 are expected to be from flavour cues. The approach to maintain this behaviour for both adult

218 and paediatric formulations may not be the best design approach since differences in
219 preferences would likely exist at different ages.

220 These results have demonstrated that tribology can detect differences in oral liquid
221 medicines which may relate to mouthfeel. There are also further opportunities to use
222 tribology in a wider range of oral medicines including orally disintegrating tablets, chewable
223 tablets, oral films and gels.

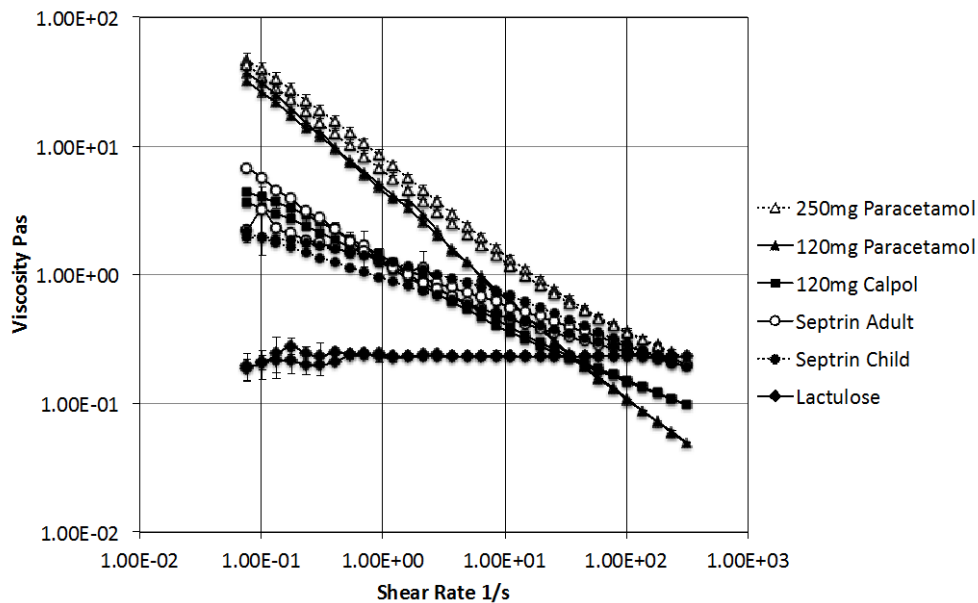


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225 Figure 1. Stribeck curves (coefficient of friction versus speed) of measured samples.

226 Data points are mean values with error bars representing 1 standard deviation

227



228

229 Figure 2. Viscosity measurements of samples over a shear rate range of 0.01 to 1000
 230 s^{-1} . Data points are mean values with error bars representing 1 standard deviation

231

232 3.2 Particle size and shape

233 Figure 3 shows representative images of each of the products viewed with the microscope.

234 The mean particle size of the 4 largest particles present in each product was measured
 235 manually via the scale bar from at least 3 representative images. This technique provides a
 236 simple means of measuring the particle size of the largest particles present in each product,
 237 as the larger particles are likely to dominate mouthfeel.

238 The results in Table 1 compare the mean particle diameter for the largest particles observed
 239 as well as the standard deviation of each.

240 Table 1. Particle size information of the suspension products tested

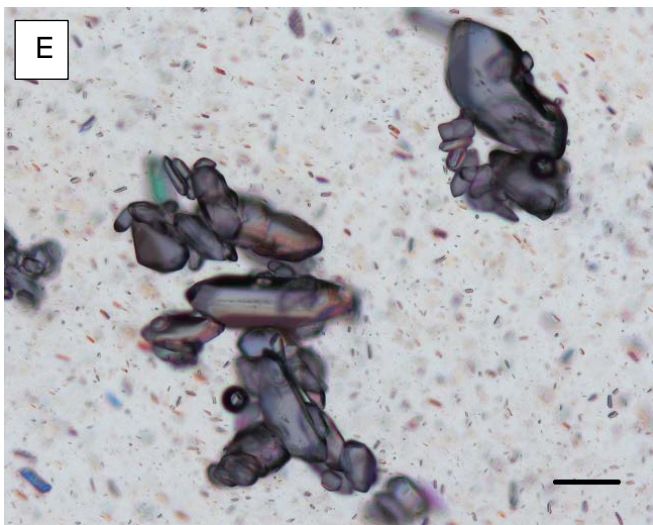
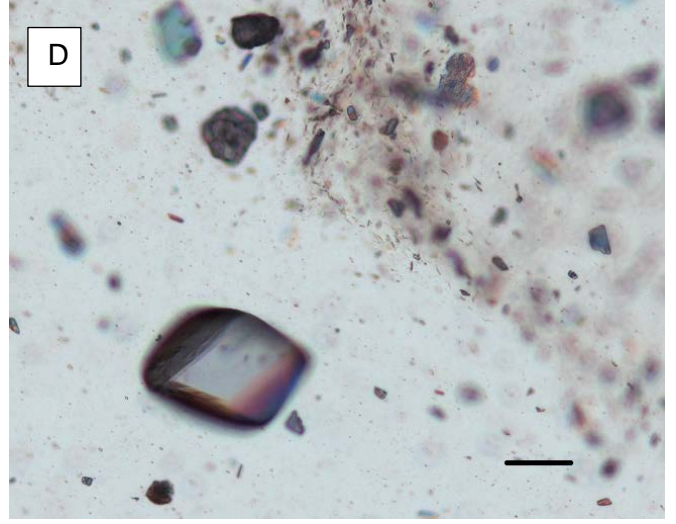
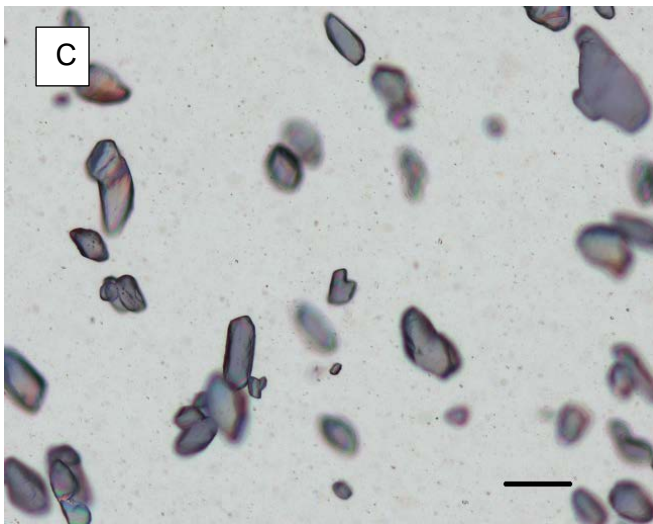
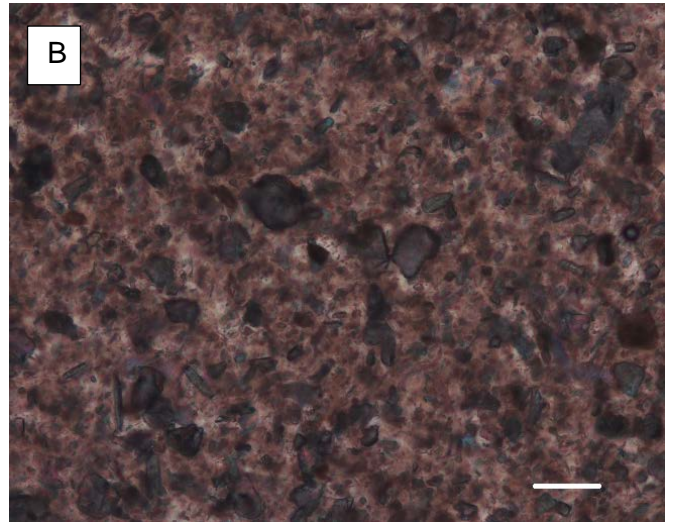
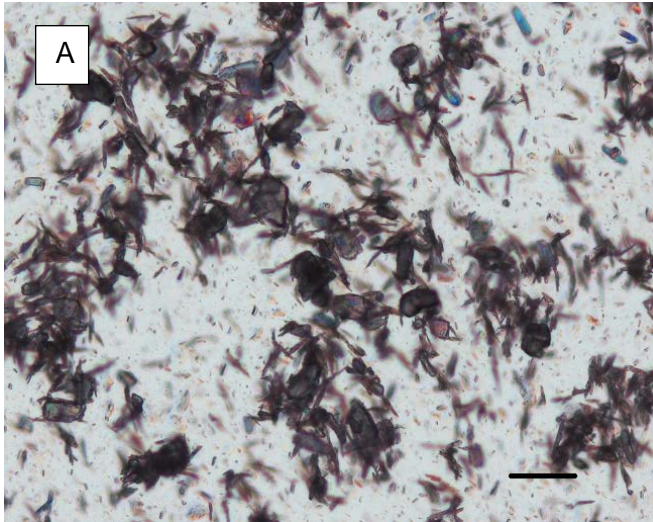
Product	Mean diameter (μm)	Standard deviation (μm)
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Septrin® Paediatric suspension 40mg/200mg per 5mL (Aspen)	25.28	8.65
Septrin® adult suspension 80mg/400mg per 5mL (Aspen)	36.90	8.25
Generic paracetamol sugar free oral suspension 120mg per 5mL (Edict)	50.56	12.41
Generic paracetamol sugar free oral suspension 250mg per 5mL (Pinewood laboratories)	48.33	19.79
Calpol® paracetamol sugar free oral suspension 120mg per 5mL (McNeil)	69.72	38.89

241

242 The particle size varied between products, as did the number of particles present. However,
 243 Calpol® contained particles of the largest dimensions (although not statistically significantly
 244 larger ($p > 0.05$) in this estimated methodology) yet there are no mouthfeel issues associated
 245 with this product. This may also be due to the taste being the most important factor, which
 246 masks potentially problematic mouthfeel. All products had particles greater than 2 μm which
 247 was previously reported as detectable in food by trained adult panels (Engelen et al.,
 248 2005a). However, it may be expected that medicines contain particles and grittiness may not
 249 be reported as an issue in such products.

250



257 Figure 3. Representative images of the products ((A) = Septrin® Paediatric suspension
258 40mg/200mg per 5mL (Aspen); (B) = Septrin® adult suspension 80mg/400mg per 5mL
259 (Aspen); (C) = generic paracetamol sugar free oral suspension 120mg per 5mL (Edict); (D) =
260 generic paracetamol sugar free oral suspension 250mg per 5mL (Pinewood laboratories)
261 and (E) = Calpol® paracetamol sugar free oral suspension 120mg per 5mL (McNeil)) used to
262 calculate the diameter of the largest particles present. Scale bar = 50µm.

263 **4 Conclusions**

264 These results highlight the use of tribology as a tool to understand lubrication processes
265 involving oral liquid medicines and the unique information it can provide. However, like any
266 physical *in vitro* technique, it is still difficult to directly relate tribological measurement to
267 sensory perception and developments therefore additional work is required to better utilise
268 sensory panel and *in vitro* data from a range of measurements for future products. The
269 application of tribology in this context has the potential to add value to the design process by
270 allowing measurements at a different scale to rheology and more traditional methods. This
271 could play a crucial role in the rational design of oral liquid medicines with high consumer
272 acceptability.

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