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

Hannah Batchelor<sup>1</sup>, Rebecca Venables<sup>2</sup>, John Marriott<sup>1</sup> and Tom Mills<sup>3</sup>

1. Pharmacy and Therapeutics Section, School of Clinical and Experimental Medicine,  
College of Medical and Dental Sciences, Medical School Building, University of  
Birmingham, Edgbaston, B15 2TT
2. School of Pharmacy, Hornbeam Building, Keele University, Keele, Staffordshire, ST5  
5BG
3. School of Chemical Engineering, University of Birmingham, Edgbaston, Birmingham,  
B15 2TT

Corresponding author: Hannah Batchelor. Email: h.k.batchelor@bham.ac.uk

Pharmacy and Therapeutics Section, School of Clinical and Experimental Medicine, College  
of Medical and Dental Sciences, Medical School Building, University of Birmingham,  
Edgbaston, B15 2TT

Phone: +44 (0)121 414 3717

## **Abstract**

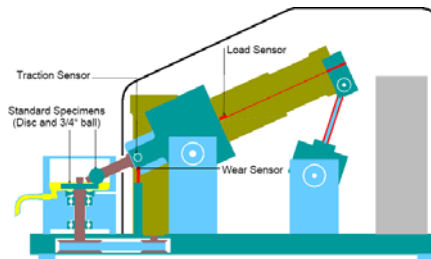
The palatability of medicines is likely to have a significant impact on patient adherence and consequently, on the safety and efficacy of a medicinal product. Palatability encompasses properties of medicines not limited to taste including swallowability (e.g. size, shape,

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

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

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

### Graphical abstract



**Medicine → Tribology → acceptability**

## 1 Introduction

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

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

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

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

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

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

In terms of application of tribology to liquid medicines in the mouth we are mostly interested 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  $\mu\text{m}$  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



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

## 2.4 Particle size and shape

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

## 3 Results and discussion

### 3.1 Tribology and rheology

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

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

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

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

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

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

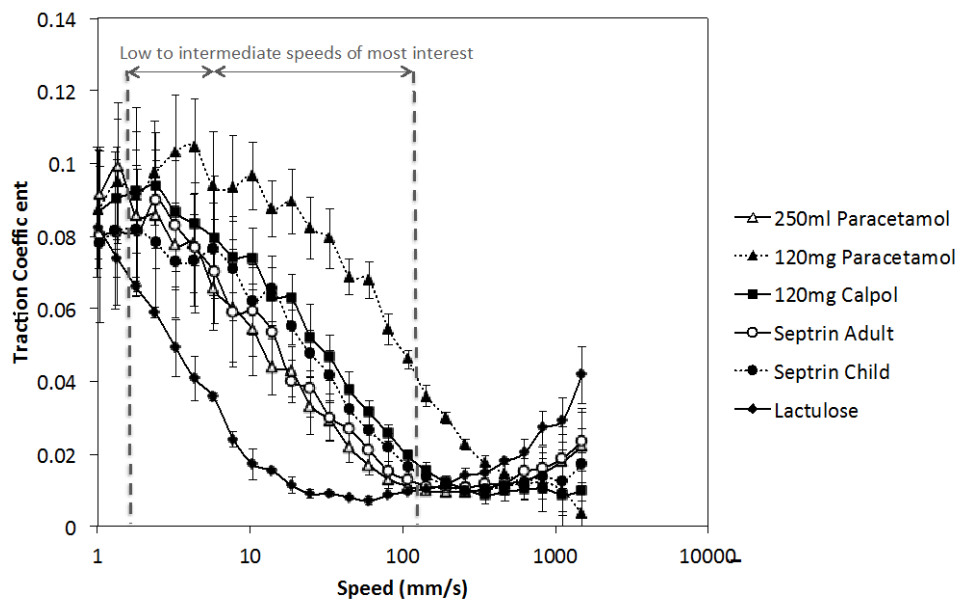


Figure 1. Stribeck curves (coefficient of friction versus speed) of measured samples.

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

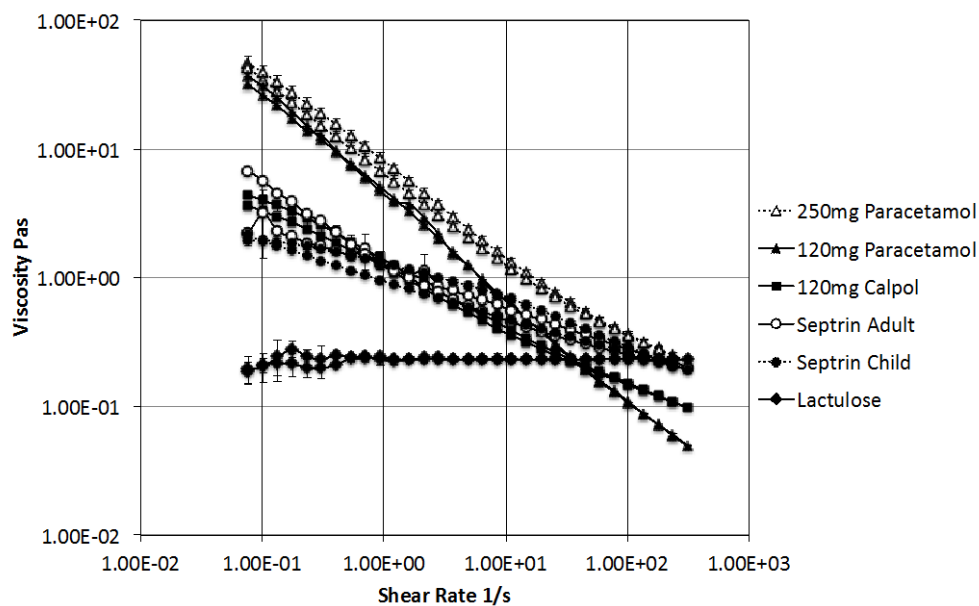


Figure 2. Viscosity measurements of samples over a shear rate range of 0.01 to 1000  $\text{s}^{-1}$ . Data points are mean values with error bars representing 1 standard deviation

### 3.2 Particle size and shape

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

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

Table 1. Particle size information of the suspension products tested

Product	Mean diameter ( $\mu\text{m}$ )	Standard deviation ( $\mu\text{m}$ )
---------	---------------------------------------	--

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  $\mu\text{m}$  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.

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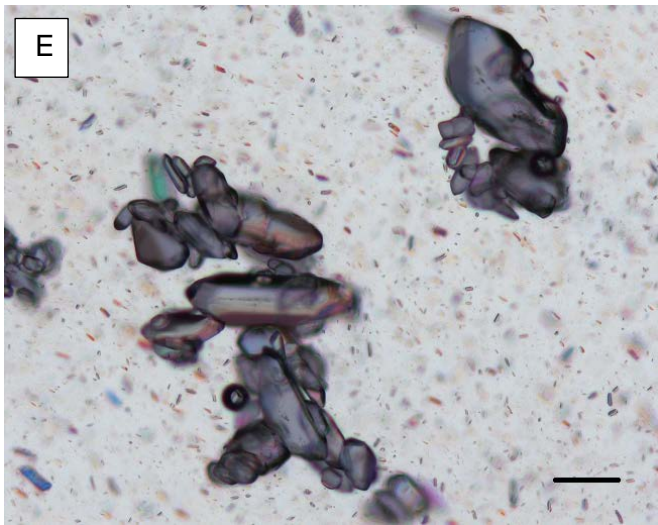
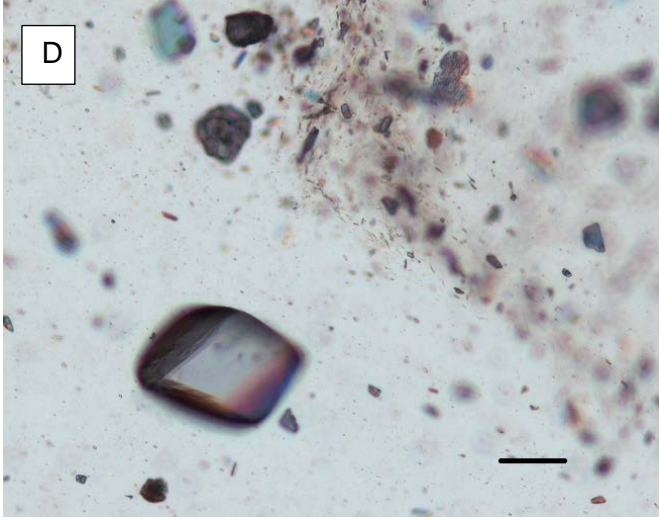
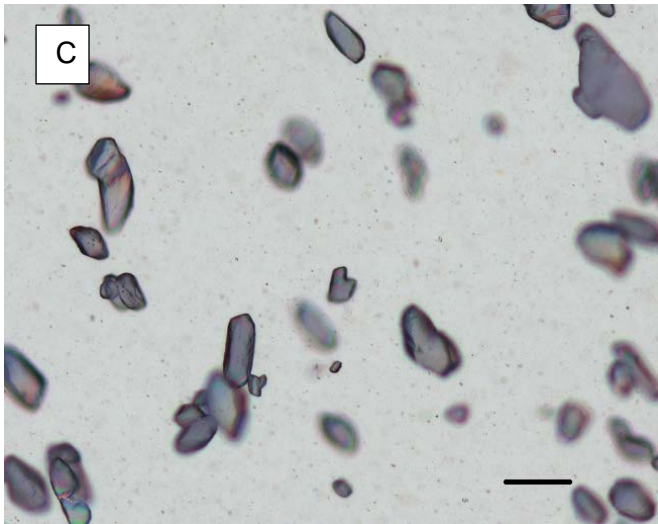
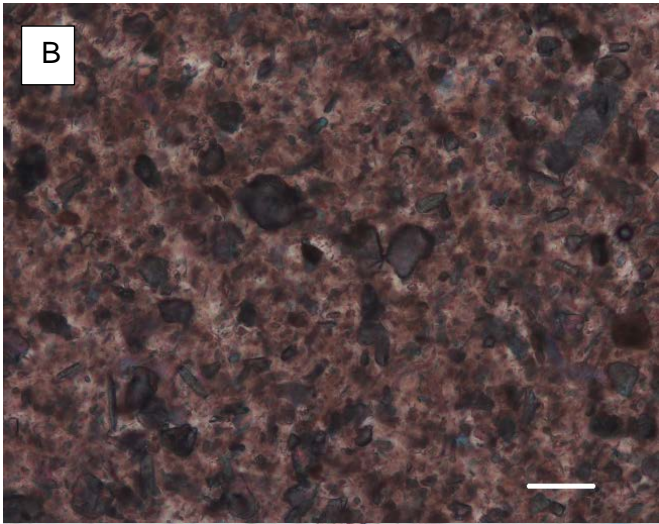
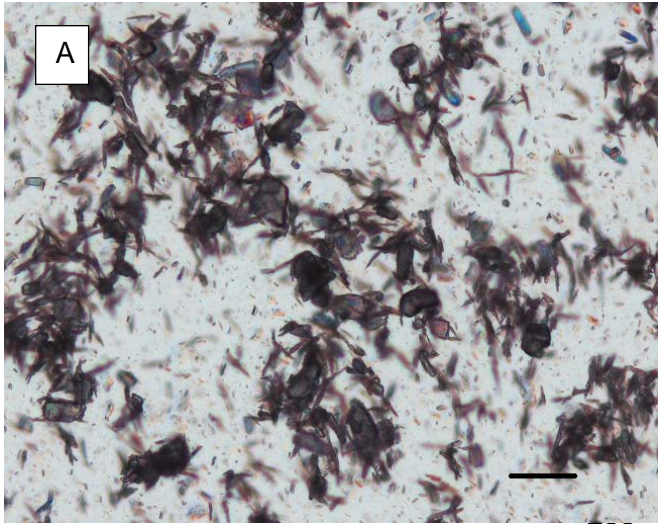


Figure 3. Representative images of the products ((A) = Septrin® Paediatric suspension 40mg/200mg per 5mL (Aspen); (B) = Septrin® adult suspension 80mg/400mg per 5mL (Aspen); (C) = generic paracetamol sugar free oral suspension 120mg per 5mL (Edict); (D) = generic paracetamol sugar free oral suspension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

#### 4 Conclusions

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

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