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Title: Tribology provides an *in vitro* tool that correlated to *in vivo* sensory data on the mouthfeel of coated tablets

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Abstract:

Tribology is an emerging technique in the pharmaceutical field for texture and mouthfeel studies. Due to its relevance to oral sensory perception, tribology supports the development of novel products in the food industry. This study explores tribology as a tool to optimise the mouthfeel and ease of swallowing of pharmaceutical coatings and coated tablets. We measured the lubricating properties of eight pharmaceutical coatings using two methods: surface tribology and thin film tribology. As food science is more advanced in texture and mouthfeel studies, methods were developed from this field with the intention to mimic tablet ingestion. Further, the link between tribological measurements and the sensory evaluation of the coated tablets obtained by a human panel was explored. We have demonstrated that discrimination of tablets with different coatings using tribology is feasible. The viscosity, solubility and composition of the coating formulations played an important factor in lubrication. For the first time, tribology was used to analyse the lubricating properties of conventional tablet coatings and a linear relationship between tribology and the oral sensory perception, i.e. slipperiness and stickiness, was demonstrated. Tribology has the potential to become a valuable formulation tool to characterise the lubricating behaviour of coated tablets in the context of oral sensory perception.

Key words: tribology, tablet coating, coefficient of friction, slipperiness, stickiness

1 Introduction

Tribology data supports the development of novel products in the food industry based on its relevance to oral sensory perception; such a tool is useful in the development of pharmaceutical formulations to optimise their mouthfeel and ease of swallowing. Both mouthfeel and ease of swallowing of medicine contribute to the patient acceptability of a solid oral medicinal product (EMA, 2013; EMA, 2017). To optimize mouthfeel of medicines, *in vitro* methods are of particular interest, due to their reproducibility, low-cost and applicability in early product development.

Despite the number of sensory textural attributes that patients perceive while taking oral medicines, like slipperiness (Hofmanová et al., 2019), hardness/softness (Paradkar et al., 2016), grittiness (Lopez et al., 2016), adhesiveness (Scarpa et al., 2018) and others (Uchida et al., 2013) research into

medicine mouthfeel is limited. The use of *in vitro* tools that measure textural characteristics of a product would improve mechanistic understanding of factors that affect how texture is perceived. For solid formulations which are swallowed intact (e.g. conventional tablets) the sensations are triggered by an interaction between the solid oral dosage form (SODF) and oral surfaces – tongue, cheeks, teeth, and palate. This interaction is modulated by the saliva or water with which the medicine was taken. The presence of a coating and interaction of the tablet with saliva further affects oral perception: an uncoated tablet may give a feeling of dryness due to saliva absorption, while a water-soluble coating in contact with saliva may induce slippery or slimy sensations. While direct measurement of textural sensations within the mouth is impossible, the *in vitro* study of oral textural phenomena is based on mimicking surface interactions within the mouth. Tribological measurements are considered the most appropriate method to study oral textural phenomena related to solid medicines. Difficulties in swallowing medicines are often attributed to the size of a SODF (Schiele et al., 2013), however, reducing the formulation size is not always possible. In such a case, increasing surface slipperiness is a viable solution (Mahdi and Maraie, 2015). Slipperiness is related to the resistance to motion when sliding over an oro-oesophageal surface (Seo et al., 2007), hence, a tablet which has low resistance to movement should be easy to swallow. Application of a coating modifies the tablet surface; thus, the movement of a tablet through the mouth and oesophagus can be facilitated with a slippery coating or impeded if the coating is sticky.

To predict the ease of swallowing and/or oesophageal transit of tablets previous studies have used a sliding movement to mimic the passage of a tablet through the oesophagus and measured the force needed to pull a sample over a surface of mucus or oesophageal tissue (Drumond and Stegemann, 2019; Smart et al., 2015). The authors screened a number of materials commonly used for tablet coating: polymers, plasticised polymers and waxes using coated discs (glass or polyethylene) instead of tablets. These methodologies were not correlated with *in vivo* studies.

Tribology is the science of friction and lubrication of surfaces in relative motion. It is of particular interest to the study of tablet slipperiness due to its relevance to oral perception. Tribological studies of friction and behaviour of food products have been linked with the human perception of slipperiness, roughness, grittiness and other mouthfeel attributes (Sarkar and Krop, 2019). Tribology enables the study of a product's microstructure and the behaviour of individual components (e.g. particles or droplets) and so, has been used to guide the design of food products with desired mouthfeel properties. In general, it is accepted that while tribology does not provide a direct representation of processes in the mouth, it can offer valuable information on material behaviour. In the pharmaceutical field, tribology was introduced by Batchelor et al. (2015) with a paper describing the friction behaviour of oral syrups and suspensions, while Mahdi et al. (2016) applied tribology to test topical gel formulations. A more recent study applied tribology to measure orally disintegrating films, but only as a supplementary testing method (Łyszczarz et al., 2020).

In brief, the principle of tribology lies in measuring the coefficient of friction (COF, μ) between two surfaces in relative motion. The instrument (a tribometer) is specifically designed to be relevant to oral friction and reflect oral conditions including force, speed, movement, lubricant and the choice of surfaces (Pradal and Stokes, 2016). The interpretation of results involves analysis of the whole measuring system, as COF is a system property, not a material property. The coefficient of friction is inversely related to slipperiness, and so relevant to the human perception of what is "slippery" (Pradal and Stokes, 2016). In the field of food research two complimentary approaches have been taken to measure product slipperiness: direct measurement of the solid sample surface (surface tribology) and thin film measurements using liquid samples (thin film tribology).

Surface tribology measures static and dynamic COF, which represent the forces needed to start or continue the sliding movement of a sample over a surface, respectively; the presence of a lubricant is optional. In this method a whole tablet sample can be used, so it informs about the lubricating properties and wear of the tablet surface. Thin film tribology evaluates the friction of liquid samples (used as a lubricant); it is relevant to measure lubricity of a dispersed tablet coating, which reflects how a coating dissolves in the mouth. Thin film tribology evaluates the capability of a lubricant to reduce friction (lubricity) by measuring the COF of two interacting surfaces at a range of speeds. The resulting data are presented as a Stribeck curve, where COF is a function of sliding speed (v_s) and lubricant viscosity (η_{eff}). To date, no other studies have investigated tablet coatings using thin film tribology.

Analogous to food sciences, the tribological measurements of tablets (and dispersed tablet coatings) can be correlated with *in vivo* data. Once a correlation has been demonstrated, tribology could be used to screen for favourable textural qualities, and so inform the manufacture of oral formulations with optimised sensory properties. The objective of the present study is to (i) evaluate the surface tribology and thin film tribology as a tool to differentiate between tablet coatings and (ii) to explore the link between the tribological measurements and sensory evaluation obtained by a human panel for coated tablets.

2 Materials and methods

2.1 Preparation of coated tablets

Two types of tablet core were used: convex round (T_R), 7 x 3 mm, and convex oval (T_O), 19 x 9 x 7 mm. The round cores, T_R, comprised quinine sulfate at 2.5% w/w (Sigma-Aldrich, USA) and directly compressed powder (Firmapress, Oxfordshire, UK) composed of microcrystalline cellulose, magnesium stearate, silica dioxide and di-calcium phosphate. T_R tablets were compressed using a MiniPress single punch tablet press type MII (Riva S.A, Argentina) with an average force of 15 kN (average mass 212 mg, disintegration time 1 minute 14 seconds, hardness 81 N, friability 0.1%). The oval cores, T_O, comprised lactose, starch, microcrystalline cellulose, and magnesium stearate and were prepared by direct compression (average mass 951 mg, disintegration time 1 minute 53 seconds, hardness 125 N, friability 0.1%). T_O tablets were supplied with a statement of fitness for human consumption by VerGo Pharma Research Laboratories Pvt. Ltd.

The immediate release film coatings selected for this study represented a range of available materials with varying physico-chemical properties. The following materials were used to prepare the coatings: HPMC 5 (Biogrund GmbH, Germany), Eudragit® EPO readymix (Evonik, Germany), glycerol (Sigma-Aldrich, USA), talc (Scientific Laboratory Supplies Ltd, UK), titanium dioxide (Fisher Scientific, UK), xanthan gum (Sigma-Aldrich, USA), Lubritab® (JRS PHARMA, Germany), Capmul® MCM (ABITEC Corporation, USA), Surelease® (Colorcon, USA), Opadry® 03F (Colorcon, USA), Opadry® EZ Swallow white (Colorcon, USA), Opadry® EZ Swallow clear (Colorcon, USA). Table 1 lists the composition of the tablet coatings used.

The coating suspensions were prepared as per Table 1. The T_O tablet cores were coated by the manufacturer under good manufacturing practice conditions (coating equipment: NEOCOTA 40D dual pan coater). The T_R tablet cores were coated in the fluid bed coater (Caleva Mini Coater 2, Dorset, UK) under the following conditions: pump 1.6 rpm, fan 16 m/s, agitation 15.2 Hz and temperature 60°C. The coating level was controlled by weighing the batch of tablets until 4% weight gain was achieved. The tablets were evaluated for their lubricating properties using surface tribology.

2.2 Preparation of the coating films dispersed in distilled water

First, coating suspensions (same as for tablet coating) were sprayed onto an acetate sheet with a spray gun (Caleva Mini Coater 2, Dorset, UK), with continuous drying at 60°C, until a 200 µm thick film was achieved; the coating film was then cured at 40°C for 2h. Then, the coating film was dispersed in distilled water to a concentration of 5 mg/mL and its lubricating properties were tested the next day to ensure the dispersed polymer was fully hydrated. The concentration of the coating was calculated to match the one that can be achieved when the tablet coating dissolves/disperses in the mouth (calculated as an average mass of coating on a tablet divided by volume of saliva at rest). The samples of dispersed coatings are referred to as Coat-1_{dis}, Coat-2_{dis}, Coat-3_{dis}, etc. to distinguish from the tablet samples. Dispersed coatings were evaluated for their lubricating properties using thin film tribology.

2.3 Surface tribology

The experiments were performed using a rheometer with a tribo-rheology cell (Discovery HR-2, TA Instruments, USA) adapted for the tablet measurement (Figure 1a, b). Top geometry: three tablets (a minimum number to obtain stable geometry) were mounted on the flat top plate of the probe with cyanoacrylate glue (a reproducible positioning was ensured using a custom 3D-printed mould). The probe was equipped with a beam coupling that self-aligned the two surfaces under test to ensure uniform contact and axial force distribution. Bottom geometry: Transpore™ surgical tape (3M™) was attached to the bottom surface to model the asperity of the tongue (Nguyen et al., 2016) (the tape proved to be discriminatory in developmental experiments, see Supplementary data - Figure S.1).

Prior to the experiment the top and bottom surfaces were brought into contact and a 2 N load was applied. 2 N was chosen to provide contact pressures relevant to oral processing, 1 – 3 N (Valentim et al., 2016), while maintaining repeatable, discriminatory data. Lubricant, distilled water, was added at t = 0 s. The top surface (with attached tablets) rotated with increasing speed from 0.001 to 1 rad/s^{-1}. The temperature was controlled at 25 °C, as ambient temperature is more representative for the product compared to body temperature (37 °C) due to the short oral residence time. The details of the methodology are shown in Table 2. The resulting data were screened to exclude data points where the load force exceeded ±10% of the set value. Each experiment was performed in quadruplicate.

2.4 Thin film tribology

The experiments were performed using a rheometer with a tribo-rheology cell (Discovery HR-2, TA Instruments, USA) (Figure 1a, c). Top geometry: 3-balls-on a plate; bottom geometry: Tegaderm™ hydrocolloid thin dressing (3M™) was attached to the bottom surface (the dressing proved to give well defined Stribeck curve and was discriminatory in developmental experiments, see Supplementary data - Figure S.2).

Prior to the experiment the top and bottom surfaces were brought into contact and 1 N load was applied. 1 N was chosen to provide contact pressures relevant to oral processing, 1 – 3 N (Valentim et al., 2016), while maintaining repeatable, discriminatory data. Then 4 mL of dispersed coating at a concentration 5 mg/mL (used as a lubricant) was added to the cup at t = 0 s. The top surface rotated with increasing and decreasing speed from 0.001 to 10 rad/s^{-1}. The temperature was controlled at 25 °C (Table 2). COF vs. sliding speed curves (µ versus v_s) were obtained in 6 consecutive sweeps, with the sliding speed first increasing, and then decreasing in a stepwise logarithmic mode. Due to variability, the first curve was discarded. The data were screened to exclude data points where the load force exceeded ±10% of the set value. Each experiment was performed in quadruplicate.

Thin film measurements provided data as a function of COF vs. sliding speed (μ versus v_s), which were recalculated including effective viscosity (η_{eff}) to obtain a Stribeck curve (μ versus $v_s\,\eta_{eff}$). Effective viscosity represents the viscosity of the sample under test at the contact area during the COF measurement. As η_{eff} cannot be directly measured, an estimate is usually used, i.e. the minimal value of viscosity (η_{min}) at high shear rate (>100 s^{-1}) (de Vicente et al., 2005). The data presented was plotted as Stribeck curves.

2.5 Viscosity of the coating films dispersed in distilled water

The viscosity of dispersed coatings at concentration 5 mg/mL was measured using a 40 mm parallel plate geometry with a 1 mm gap (Discovery HR-2, TA Instruments, USA). The data were collected in six consecutive logarithmic sweeps at shear rates increasing and decreasing from 0.01 to 1000 s^{-1}. Testing temperature: 25 °C; sample volume: 1.25 mL. Samples were analysed in quadruplicate. Viscosity at specific shear rates, e.g., viscosity at a 50 s^{-1} shear rate (η_{50}), were reported. The effective viscosity ($\eta_{eff} = \eta_{min}$) was determined to be the minimal value of viscosity obtained at a high shear rate, i.e., between 100 - 1000 s^{-1} (de Vicente et al., 2005).

2.6 Sensory evaluation

During sensory evaluations participants (83 healthy untrained adults between the ages of 18 and 75 years) assessed (i) ease of swallowing and (ii) sensory attributes of T_O tablets as detailed in Hofmanová et al. (2019). During the evaluation of ease of swallowing, the participants were presented four tablets (T_O, T_OCoat-6, T_OCoat-7, T_OCoat-8) in a randomised order, the participants swallowed tablet samples, one by one, in their usual manner, with unlimited access to room temperature spring water. After each sample, they assessed the ease of swallowing on 100 mm visual analogue scale (VAS). During the evaluation of sensory attributes, the participants were presented with same four tablets in a randomised order, the participants were asked to hold the tablet in their mouth for a minimum of 10 seconds and feel the tablet surface with their tongue and palate, then spit or swallow the tablet according to their preference. After each sample, they assessed tablet roughness, adhesiveness and slipperiness using 100 mm VAS. A palate cleanser was given before each sample, i.e. drinking room temperature spring water, followed by a piece of lightly salted cracker (Jacob's, or Schar gluten-free) and followed again by room temperature spring water (Lucak and Delwiche, 2009).

2.7 Data analysis

Pearson's correlation coefficient (r) and Spearman's correlation coefficient (r_S) were used to assess the strength and direction of correlation between *in vitro* and *in vivo* variables. The average for each *in vitro* and *in vivo* variable was calculated and used in the correlation. For surface tribology data three characteristic points were analysed: static friction (I) at beginning of test (COF_{static}), slip region (IIA) at t = 10 seconds (COF_{10}) and high friction region (IIB) at t = 30 seconds (COF_{30}) (Figure 2). The correlation coefficients were calculated for all the T_O tablet samples, in addition for a sub-set of just the coated tablets (T_OCoat-6, -7, -8). For thin film data, all COF values at sliding speeds were analysed. Data analysis was carried out using SPSS statistical software version 26 (IBM Corp.).

3 Results

3.1 Surface tribology

The surface tribology experiment was designed to observe static and dynamic COF of tablet movement on a lubricated surface; a typical COF vs. time curve is depicted in Figure 2. In the static

friction region (I), the instrument detected the friction force required to initiate movement. Once the tablet started moving, the friction reduced (IIA). The presence of lubricant in the system (distilled water) caused dissolution of the tablet coating, which altered lubrication and further decreased the COF. Eventually, the interaction of the tablet and the bottom surface led to wear of the coating. Lack of coating at the contact area resulted in higher COF (IIB), at this point the rough surface of the tablet core directly interacts with bottom surface.

On the COF vs. time plots (Figure 3) the static and dynamic friction regions could be identified for the tablets with an HPMC-based water soluble coatings (T_RCoat-1–3). In contrast, for the tablets with water-insoluble coatings (T_RCoat-4 and T_RCoat-5, based on basic butylated methacrylate copolymer, and ethyl cellulose, respectively) the shape of the COF vs. time curve did not include the characteristic regions (I, IIA, and IIB) shown in Figure 2. At the beginning of COF vs. time plots, an increase in COF was observed. The COF for these samples was comparable, or higher than for the uncoated tablet (T_R).

Observed differences between T_R tablets demonstrated the feasibility of the method to differentiate between tablet coatings and gave a premise to apply surface tribology to assess *in vitro* whether experimental formulations (T_OCoat-7, Opadry® EZ Swallow white, and T_OCoat-8, Opadry® EZ Swallow white and clear, Colorcon®) have enhanced slipperiness as compared to a standard coating (T_OCoat-6, HPMC-based coating Opadry® 03F white, Colorcon®) or an uncoated tablet (T_O) that was used as a reference. Indeed, the formulations T_OCoat-7 and T_OCoat-8, when compared with T_OCoat-6, showed lower static friction (region I), as well as lower dynamic friction (IIA region) (Figure 4). Plus, the low friction in IIA region lasted longer for coatings with enhanced slipperiness (T_OCoat-7, T_OCoat-8). The lack of coating resulted in higher COF of formulation T_O. For this sample, most of the data points lay outside ± 10% of set load force value (Figure 4), hence, data presented for T_O included all data points collected. Poor force reproducibility for the T_o sample was attributed to fast water absorption and disintegration of the tablet which prevented the tribometer from maintaining the applied force.

3.2 Thin film tribology

The thin film tribology experiment was designed to observe changes of lubricity of a dispersed film coating under a range of speeds. The resulting data are plotted as a Stribeck curve, where COF is a function of sliding speed (v_s) and lubricant viscosity (η_{eff}). Along the Stribeck curve, three lubrication regimes can be identified.

- Boundary regime: at the lowest speeds, where there is no or minimal lubrication between surfaces, and the COF depends on surface properties; this regime has been linked to astringency (Rossetti et al., 2009) and slipperiness (Malone et al., 2003; Prakash et al., 2013).
- Mixed regime: at intermediate speeds, where the lubricant becomes entrained within the contact area and creates a thin layer – 'thin film' – between the surfaces and the surface contact remains only on the larger asperities; as more lubricant is entrapped, friction gradually decreases; this regime has been linked to slipperiness (Malone et al., 2003; Prakash et al., 2013) and creaminess (Chojnicka-Paszun et al., 2012).
- Hydrodynamic regime: at the highest speeds, where both surfaces are separated by a continuous layer of lubricant; at this point, the friction depends on the lubricant viscosity and its overall structure.

Figure 5 shows the Stribeck curves obtained for distilled water (as a control) and samples Coat-1_{dis} – Coat-8_{dis} at a concentration of 5 mg/mL. The regions of a boundary, mixed and hydrodynamic regimes are depicted. For several samples boundary and mixed regimes were non-distinguishable in

this tribological set-up (Coat-2_{dis}, -7_{dis}, -8_{dis}). Water is a poor lubricant (high COF values observed) because a water film is easily disrupted, impeding full film lubrication; all samples of dispersed coatings enhanced lubrication when compared with water.

3.3 Viscosity of the coating films dispersed in distilled water

Viscosity data from the tested tablet coating samples are presented in Table 3. To allow comparison between samples, a 50 s^{-1} shear rate regarded as representative of within the oral cavity (He et al., 2016) was used. The highest viscosity was observed for samples containing thickening polysaccharides (Coat-3_{dis}, Coat-7_{dis}, Coat-8_{dis}). The least viscous coating samples were from the lipid-based formulation (Coat-2_{dis}) and the insoluble polymer formulation (Coat-5_{dis}). For each sample, the minimum viscosity (η_{min}) at high shear rates (≥100 s^{-1}) is given; these values were used to estimate the effective viscosity ($\eta_{eff} = \eta_{min}$), required to plot Stribeck curves for thin film tribological data.

3.4 Correlation with sensory data

The participants' average VAS scores for ease of swallowing and mouthfeel attributes are presented in Figure 6. The three coated tablets (T_OCoat-6–8) were described as easier to swallow, slippery, smooth and less sticky, as compared to the uncoated tablet. Based on the rank order of *in vivo* and *in vitro* data a good correlation was achieved for ease of swallowing, slipperiness and stickiness (Table 4). A high level of correlation was achieved based on Pearson's correlation coefficient values when all tablet samples were included. However, analysis of data point distribution (Figure 7) revealed similarity in VAS scores and COF values of the coated tablets when compared to the uncoated one. This clustering of data points led to an artificially high Pearson's correlation coefficient value. Therefore, a correlation coefficient was also calculated which only included coated tablets and two significant linear correlations were found. The COF_{30} of coated T_O tablets correlated strongly with slipperiness, while COF_{10} with stickiness.

4 Discussion

4.1 Mechanistic explanation of friction properties of coated tablets and dispersed coatings

A critical feature of a useful tribological method is the ability to distinguish between samples; the friction pattern of tested samples confirmed the effectiveness of surface and thin film tribology as tools to differentiate between coated tablets and tablet coatings, respectively. The lubrication behaviour of the samples tested is discussed below according to their composition (Table 1) and behaviour in water (Table 3).

4.1.1 Impact of viscosity modification on lubricity

Polymers with thickening efficiency, like HPMC or polysaccharides, form hydrocolloids in water (Table 3). This leads to increased viscosity and elasticity of aqueous solutions which encourages lubricant entrainment into the contact area and favours lubricant retention resulting in improved lubricity (de Vicente et al., 2006; Stokes et al., 2011). We observed such behaviour; even a low concentration of polymer considerably improved lubrication (compared to pure water), as shown by a low COF for the mixed regime for Coat-1_{dis}, Coat-6_{dis} (both HPMC-based) and Coat-3_{dis} (HPMC + xanthan gum-based). A similar phenomenon has been reported previously for polymers in aqueous solutions which exhibit viscoelastic behaviour (de Vicente et al., 2005). The lubricity improved with increasing polymer concentration, as demonstrated by not only on Stribeck curves (Figure 5 a, c) but also as a decrease of static friction (region IA) (Figure 3, compare T_RCoat-1 vs. T_RCoat-3). Viscosity modification also explains the decrease in COF during the tablet testing observed for T_RCoat-1,

T_RCoat-3 and T_OCoat-6 (region IIA). In contact with water, the HPMC and polysaccharides present in these coatings formed a colloid at the interface of a tablet and bottom geometry which enhanced lubrication. After the coating had worn off the value of COF increased (region IIB). Viscosity, however, cannot fully explain friction behaviour, for example, despite the similar viscosity, Coat-7_{dis} and Coat-8_{dis} showed higher lubricity than Coat-3_{dis}, which was attributed to medium-chain triglycerides (MCT) content.

4.1.2 Lubricity of emulsion-based formulations

In accord with Smart et al. (2015) lipid-containing coating formulations (T_OCoat-7, T_OCoat-8 comprising MCT, T_RCoat-2 containing hydrogenated cottonseed oil) provided good lubrication. Unlike tablets coated with other formulations, tablets with the lipid-based coating maintained low friction for the entire duration of the test (Figure 3). Improved lubricity was also observed in thin film tribology tests; low COF values were observed even at low speeds (Figure 5), with negligible differences between shapes of Stribeck curves. When dispersed in water all lipid-based coatings (Coat-2_{dis}, -7_{dis}, -8_{dis}) formed oil in water (o/w) emulsion. O/w emulsions exhibit a reduction in friction determined mainly by deposition of oil droplets on the surfaces (Dresselhuis et al., 2008b). As more oil droplets adhere and spread on the surface, they coalesce forming a film. Although, under the test conditions (i.e. where the coating was dispersed in water) only an unstable emulsion could be formed which was favourable for lubricity. Research has shown that less stable emulsions better lubricate hydrophobic surfaces, as they are more likely to coalesce (Dresselhuis et al., 2007). This is also likely to be the case *in vivo* when the coating dissolves in the mouth.

4.1.3 Effect of large water insoluble particles on lubrication

The presence of particles affects friction, both in terms of shape and amount of the particles (Taylor and Mills, 2020); irregular particles can increase, while spherical decrease friction as an effect of 'ball-bearing' behaviour (Yakubov et al., 2015). We observed that insoluble polymer coatings (formulations T_RCoat-4 and T_RCoat-5) broke up under shear forces and water pressure and formed large solid flake-like particles. In consequence, for surface tribology, an instant increase of COF was observed. This differed from the findings of Smart et al. (2015) where coated discs rather than tablets were used and hence the coatings were not subjected to the additional pressures of tablet disintegration which caused the coatings to break-up. For thin film tribology, the insoluble coating particles entrained in the contact area increased COF values particularly at intermediate and higher speeds. When particles are present in the lubricant their shape and size is crucial, as only particles small enough can be constantly entrained into a contact area. Although larger particles are generally excluded from the measurement, they may still occasionally be entrained. It is likely, that such behaviour was observed for Coat-5_{dis} based on the large standard deviation of COF and flat shape of particles (Figure 5e). The samples Coat-4_{dis} and -5_{dis} had a lower viscosity when compared with the hydrocolloid-based samples discussed earlier (Table 3). Therefore, the lubricity was additionally impaired, which was observed as a shift in the mixed regime towards higher speeds.

4.2 Observed correlations and existing knowledge

This paper describes the relationship between tribology and oral sensory perception of conventional tablets for the first time. To explain the nature of *in vitro-in vivo* correlations knowledge on processes and conditions occurring in the mouth is necessary. A correlation with surface tribology was found for stickiness at COF_{static} and for slipperiness at COF_{30}. The correlation of these attributes to COF at different time points is due to different sliding speed during the test (v_s (t_{static}) = 0.3 mm/s, v_s (t_{30}) = 4.6 mm/s). Adhesion is a component of static friction (Goryacheva and Makhovskaya, 2011) explaining the correlation found for stickiness at low speeds. In contrast, slipperiness in the mouth

assesses the dynamic friction (the relative movement of surfaces once in motion), hence the correlation at higher speeds.

Based on findings from this research, thin film tribology cannot be used as a predictor of sensory attributes but can help the understanding of mouthfeel perception. Thin film tribology (COF_B and COF_M) and sensory attribute data agreed in rank order, but correlations were not significant (Table 4). The lack of a linear correlation should not lead to dismissal of the results, instead caution should be exercised in their interpretation. The lubricity of the dispersed coatings was related to their viscosity, oil content and presence of insoluble particles which suggests that thin film tribology has potential to aid understanding of sample mouthfeel. Many previous studies explain the tribology–sensory correlation with foods in similar ways (de Wijk and Prinz, 2005; Dresselhuis et al., 2008a; Krop et al., 2019; Laguna et al., 2017; Laiho et al., 2017).

4.3 Strengths and limitations of the method

In contrast to previous research which used coated plastic/glass disks (Drumond and Stegemann, 2019; Smart et al., 2015), the surface tribology method developed allowed study of whole tablet behaviour under shear and load forces including observation of coating durability (wear). The coating level used (~3-4%) was similar to that commonly used in industry and generally employed for aesthetics and recognisability. Such a thin coating may have short durability; therefore, the oral and oesophageal surfaces could potentially be exposed to contact with a tablet core, not just the coating. Furthermore, the core properties of the tablet can affect *in vitro* friction behaviour, as core shape determines the size of the contact area with mucosa (different friction pattern of uncoated tablets – T_R and T_O). In this study, the size of T_O cores was intentionally large to reflect a tablet which is difficult to swallow and hence allow a better evaluation of the impact of a tablet's coating on ease of swallowing. The shape of tablet core will determine the volume of lubricant entrained between two surfaces as well as the dynamics of coating removal that will impact upon the measurements made, further work is required to fully explore these aspects.

The thin film tribology method used was developed from food science methodology. Therefore, liquid samples of dispersed coatings were used to resemble the tribological samples tested by food scientists. Testing coatings in this dissolved/dispersed form is advantageous in that it omits the effects of the tablet core which allows more detailed analysis of the mechanisms governing lubrication. However, immediate evaluation of dispersed films led to large variability due to the timeline involved in polymer hydration; thus evaluation following overnight storage may not be truly biorelevant although the excipients within the coating (opacifiers, dyes, oil) remain dispersed in the sample.

Both tribological methods developed were limited in bio-relevance by several factors: oral surfaces, mechanical swallowing action and lubricating solutions. Oral surfaces cannot be mimicked directly, this model used a surface intended to mimic the tongue and not any of the surrounding mucosa. In addition, the mechanical swallowing action cannot be replicated using a tribometer, as the instrument used allowed a circular rather than linear movement. The tests excluded the impact of saliva on friction, which may have an impact on oral lubrication (Bongaerts et al., 2007). The study only incorporated a limited number of tablet types: two sizes, two shapes, and eight coatings, hence is not representative of the vast array of tablet formulation possibilities. Extending the spectrum of SODF analysed by including, for example, minitablets, caplets, soft and hard capsules would be beneficial.

Only limited *in vivo* data was available for a correlation where the tablet coating samples were all similar. A future study that explored a wider range of coated tablets would provide a better data set to review the correlations presented here.

4.4 Practical implications and future work

We have demonstrated that discrimination of tablets with different coatings using tribology is feasible. These findings suggest that different tablet coatings may provide different levels of lubrication when placed in the wet oral environment. As friction is a system property it depends not only on the tablet surface properties but also on the lubricant (Taylor and Mills, 2020). Thus, it is likely that the same tablet with the same coating may be perceived differently by different patients. For instance, people suffering from xerostomia (dry mouth) or with a rougher morphology of the tongue might require a coated tablet with higher slipperiness. This implies that when testing lubrication of the coatings *in vitro*, it would be valuable to mimic the most unfavourable conditions, i.e. not only the tongue of a healthy patient but also one with a dry mouth.

In the method presented, water was used as a lubricant as other media might have changed the observed lubrication behaviours. The setting, however, allows various lubricants to be tested. It would be of future interest to test the behaviour of tablets in different liquids/semisolids taken with medications, for example juice, milk, tea, apple puree, or yoghurt, as well as artificial or human saliva.

This study showed a correlation between the COF of tablets and the human perception of slipperiness and stickiness. Although tribology cannot yet be claimed a predictive method for mouthfeel attributes, it could benefit the formulation development process as a screening tool to enable selection of optimised samples for human testing. Comparison of the two methods, surface and thin film tribology, suggests they have different potential applications. Testing coated tablets in their entirety is likely to yield results more comparable to the human perception, but the sensitivity of thin film measurements to small differences in formulation make it of use in coating development.

5 Conclusion

Tribology is an emerging discipline in the pharmaceutical field for texture and mouthfeel studies. Two *in vitro* methods developed – surface tribology and thin film tribology – were able to distinguish between different SODF coating formulations, which proved them feasible to evaluate friction of tablet coatings in context of oral processing. The viscosity, solubility and composition of the coatings played an important factor in lubrication. For the first time, the tribology was used to analyse lubricity of conventional tablets and a linear relationship between tribology and the oral sensory perception, i.e. slipperiness and stickiness, was demonstrated. While these results need to be interpreted with caution due to the infancy of the research area, they allow the mechanisms underlying the oral perception of medicines to be explored. In this way, tribology has the potential to become a valuable formulation tool to characterise the lubricating behaviour of coated tablets in the context of oral sensory perception.

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