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Tactile friction of topical creams and emulsions: Friction measurements on excised skin and VitroSkin® using ForceBoard™

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ABSTRACT

Tactile perception can be investigated through *ex vivo* friction measurements using a so–called ForceBoard™, providing objective assessments and savings in time and money, compared to a subjective human panel.

In this work we aim to compare excised skin versus VitroSkin® as model substrates for tactile friction measurements. A further aim is to detect possible differences between traditional surfactant-based creams, and a particle-stabilized (Pickering) cream and investigate how the different substrates affect the results obtained.

It was found that the difference in tactile friction between excised skin and VitroSkin® was small on untreated substrates. When topical creams were applied, the same trends were observed for both substrates, although the frictional variation over time relates to the difference in surface structure between the two substrates.

The results also confirmed that there is a difference between starch-based Pickering formulations and surfactant-based creams after application, indicating that the latter is greasier than Pickering cream. It was also shown that the tactile friction of Pickering emulsions was consistently high even with high amounts of oil, indicating a non-greasy, and non-sticky formulation. The characteristics of starch-stabilized Pickering formulations make them promising candidates in the development of surfactant-free topical formulations with unique tactile properties.

1. Introduction

Tactile perception such as greasiness and stickiness are examples of key attributes for topical skin creams. Tactile perception is a complex combination of sensory stimuli including skin stretching, pressure applied, and vibrations during touching (Ding and Bhushan, 2016), and is an elusive sensation to capture. However, several authors have noted a correlation between sensorial evaluation using trained and untrained panellists and different methods to measure skin friction (Ali et al., 2022; Egawa et al., 2002; Savary et al., 2019; Tang et al., 2015), *e.g.*, the parameter greasiness has been seen to be inversely proportional to the friction (Ali et al., 2022; Nacht et al., 1981). Lately it has been shown that tactile friction, quantified with a ForceBoard™ (Industrial Dynamics Sweden AB, Järfälla, Sweden) is often a useful descriptor of perceptual experiences, and Skedung et al. has introduced a new term - psychotribology - that merges the fields of biotribology and tactile perception (Skedung et al., 2018). Although a physical method such as tactile friction cannot describe all types of perceptions that a human panel will identify, it has some obvious advantages such as providing objective assessments and avoiding the inherent spread in results shown by a panel. It is also easier and cheaper to perform, and it focuses on one or a few parameters.

The friction of skin has been seen to be affected by humidity (Arvidsson et al., 2017; Derler and Gerhardt, 2012; Skedung et al., 2016), time of application and type of substrate used (Ding and Bhushan, 2016). Furthermore, it is also affected by the composition of the topical product such as presence/absence of occlusive components (Skedung et al., 2016), added moisturizers (Lodén et al., 1992), oil

Abbreviations: Pickering emulsions, particle-stabilized emulsions; O/w, oil-in-water (emulsions); F, friction force; L, applied load; μ, friction coefficient; SEM, scanning electron microscopy; a.u, arbitrary units.

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content (Nacht et al., 1981), and particles present (Ali et al., 2022; Timm et al., 2012).

The process of lubrication when stroking a finger over time on a body site or surface with a fluid layer has been divided into three main lubrication regimes, i.e., the "boundary", "mixed", and "hydrodynamic" regime (Guest et al., 2013). The appearance of these lubrication regimes is thought to depend on the characteristics of the applied cream and the formed film thickness. Hydrodynamic lubrication occurs during the application of the cream when the film between the finger and the substrate is thick, and friction is mainly influenced by the formulation viscosity and thickness. Subsequent spreading of the formulation and evaporation of volatile compounds leads to a residual thin film. At this stage, mixed lubrication may occur leading to a moderate increase in friction as result of the changing properties of the residue and/or the underlying surface. It has indeed been shown that hydration of the surface by an aqueous vehicle or by occluding effects can increase friction over time (Nacht et al., 1981; Tang et al., 2015). When the thickness of the residual film is reduced, lubrication resembles the boundary regime and the friction will be dominated by the surface properties of the substrate (Guest et al., 2013; Tang et al., 2015).

Lately we have observed large differences between a Pickering cream and a traditional cream (Canoderm®) when it comes to perception of tactile properties as well as tactile friction (Ali et al., 2022). Pickering creams are particle-stabilized creams and they have attracted quite some interest for providing a possibility to produce surfactant-free creams with long shelf life (Frelichowska et al., 2009b, 2009a; Marku et al., 2012; Rayner et al., 2014; Wahlgren et al., 2013).

In skin research one of the challenges is to find suitable substrates for *in vitro* investigations. Traditionally, excised porcine skin (henceforth called "excised skin") is one of the more common substrates and considered to be a good substitute for human skin (Haigh and Smith, 1994). During the last decade, several different *in vitro* skin models have been developed (Flaten et al., 2015; Van Gele et al., 2011). One driving force has been the need to avoid animal testing of cosmetic products. These models range from complex systems, like so called living skin equivalents, to fully synthetic substrates having *e.g.*, similar topography and/or lipid content as human skin. One of the synthetic models is VitroSkin® that has been successfully used in investigations of sunscreen creams (Oliveira et al., 2008) and tactile friction studies of skin creams (Skedung et al., 2016; Tang et al., 2015).

In this work we aim to compare VitroSkin® and excised skin as substrates for tactile friction measurements. A further aim is to detect possible differences between a traditional surfactant–based commercial cream (Canoderm®), and a Pickering cream and investigate how the different substrates affect the results obtained. In addition, we have performed a small study on the effect of changing the composition using Pickering emulsions. Possible effects on the results by employing two different operators were also investigated.

2. Material & methods

2.1. Materials

Canoderm® cream (ACO Hud Nordic AB, Stockholm, Sweden) was purchased from a local pharmacy. Modified quinoa starch, used as stabilizing particles in the Pickering formulations, was kindly provided by Speximo AB (Lund, Sweden). The starch was hydrophobically modified with octenyl succinic anhydride (Timgren et al., 2013).

The emollients used, medium chain triglycerides (Miglyol 812 N, IOI Oleochemical, Hamburg, Germany), isotridecyl isononanoate (Crodamol TN, Croda, East Yorkshire, England), canola oil (Akosoft 36 and Lipex Preact, AAK, Karlshamn, Sweden), jojoba oil (Natura-Tec, Fréjus, France) and triolein (Captex GTO, Abitec Co, Janesville, USA), were purchased from Barentz (Copenhagen, Denmark). Other functional excipients were carbomer (Carbopol Ultrez 30, Lubrizol, Brussels, Belgium) used as a rheological modifier, and tocopheryl acetate (Dermofeel E74, Evonik Dr Straetmans, Hamburg, Germany) used as an antioxidant. Glycerol (Sigma-Aldrich, Stockholm, Sweden) was used as a humectant. The preservatives, propyl-4-hydroxybenzoate (Propyl paraben, Solbrol P) and methyl-4-hydroxybenzoate (Methyl paraben, Solbrol M), were provided by Lanxess GmbH (Leverkusen, Germany). Milli-Q water, 18.2 MΩ cm resistivity, was used for all samples. The surfactants used were cetearyl alcohol (Nafol 1618H, Sasol Performance Chemicals, Hamburg, Germany), and PEG-100 stearate (Myrj S100) and glyceryl stearate (Cithrol GMS 40) obtained from Croda Europe (East Yorkshire, England).

2.2. Formulations

The cream formulations studied in this work include a traditional surfactant–based commercial cream (Canoderm®), a surfactant-free, particle-stabilized Pickering cream, and a surfactant-based Pickering replica (referred to as Surfactant cream). All cream formulations were oil-in-water (o/w) emulsions and were physically stable and homogenous. Rheological data of the creams have been described in a previous study (Ali et al., 2022). The Pickering cream was prepared by mixing the water-soluble and oil–soluble excipients separately. The oil phase was heated to 60 °C until all emollients were melted, and the temperature was then brought down to <45 °C. The starch was added to the water phase below 45 °C with stirring, propeller stirrer from IKA, Germany, and mixed for additional 5–10 min before slowly adding the oil-phase with stirring. The mixture was mixed for an additional 5–10 min before emulsification with a high shear mixer (IKA Ultra Turrax, Germany) at 15000 rpm for 1 min in a glass beaker.

Canoderm® was used as is without any modifications. The compositions of the three creams are shown in Table 1. The oil content of Pickering cream was 28 wt%, while the oil content in Canoderm® could be assumed to be approximately 16 wt% with a total of 8 wt% emulsifiers in the oily phase based on a recipe in a corresponding patent (SE511551C2).

The Surfactant cream was prepared in a similar way, where the oil-phase and water–phase were blended separately at 65–75 °C until all ingredients were dissolved, before adding the oil phase to the water phase while stirring with a propeller stirrer. The mixture was stirred for 5 min before emulsification with a high shear mixer at 12000 rpm for 1–2 min and allowed to cool down afterwards at room temperature.

Pickering emulsions were prepared at room temperature, according to the composition in Table 2, by mixing starch and water for 5–10 min and adding the oil with stirring and continue mixing for additional 5–10 min before emulsification with a high shear mixer (IKA Ultra Turrax, Germany) at 22000 rpm for 1 min. Emulsion droplet stabilization by starch particles was confirmed in the emulsion serum for all emulsions. However, emulsions comprising oil contents 18 wt%, 10 wt% and 5 wt% displayed creaming (Fig. S1, Supplementary information).

Table 1
Composition of creams.

Topical Cream	Ingredient list (INCI)
Pickering cream	Aqua, quinoa starch particles, caprylic/capric triglyceride, glycerol, canola oil, isotridecyl isononaoate, jojoba oil, hydrogenated coco-glycerides, carbomer, tocopheryl acetate, methylparaben, propylparaben.
Canoderm® *	Aqua, caprylic/capric triglyceride, urea, propylene glycol, hydrogenated canola oil, cetearyl alcohol, glyceryl polymethacrylate, dimethicone, paraffin, sodium lactate, carbomer, glyceryl stearate, PEG-100 stearate, polysorbate 60, lactic acid, citric acid, methylparaben, propylparaben.
Surfactant cream	Aqua, caprylic/capric triglyceride, glycerol, canola oil, isotridecyl isononaoate, jojoba oil, hydrogenated coco-glycerides, PEG-100 stearate, glyceryl stearate, cetearyl alcohol, carbomer, tocopheryl acetate, methylparaben, propylparaben.

* Composition according to ingredient list on product, and order of ingredients according to (Lodén et al., 1999).

Table 2
Composition of investigated Pickering emulsions containing triolein in (wt%).

Ingredients	Pickering emulsion 5 wt% oil	Pickering emulsion 10 wt% oil	Pickering emulsion 18 wt% oil	Pickering emulsion 26 wt% oil
Water, up to	100.0	100.0	100.0	100.0
Modified Quinoa starch	1.6	3.3	6.6	10.0
Triolein	4.8	9.8	19.8	29.8

2.3. Preparation of substrates

2.3.1. Preparation of excised porcine skin

Fresh porcine ears were acquired from a local abattoir and stored at −80 °C. The ears are residuals from food preparation, and hence ethical permission is not required. To prepare the skin substrates, defrosted porcine ears were cleaned and hair was removed with a trimmer. Full-thickness skin was excised from the inner ear using a scalpel and cut into strips (2x5 cm^2). Finally, the excised skin was wrapped in aluminium foil and stored at −20 °C until use. Before conducting tactile friction measurements, the skin was allowed to thaw and equilibrate at room temperature (at least 1 h) with a hydrated filter paper underneath.

For scanning electron microscopy, small pieces of 500 μm thick porcine skin were obtained using a dermatome (Dermatome, Integra LifeSciences, Plainsboro, NJ, USA).

2.3.2. Preparation of VitroSkin®

Vitro-Skin® (IMS Inc., Portland, ME, USA) was used as a synthetic model skin substrate. It is designed to mimic the human skin surface properties in terms of topography, pH, elasticity, surface tension, and ionic strength (IMS Inc.). The substrate (thickness ~ 127 μm) was cut into pieces of 2x5 cm^2 and placed in a desiccator above a beaker with a mixture of 85 wt% Milli–Q water and 15 wt% glycerol for 16–24 h before use according to the manufacturer's instructions. This allowed for reproducible hydration of the substrate prior to friction measurements.

2.4. Tactile friction measurements

Tactile friction measurements were performed using a ForceBoard™ (Industrial Dynamics Sweden AB, Järfälla, Sweden), following the method described by Skedung et al. (Skedung et al., 2016) with minor adjustments. The friction force (F) and applied load (L) were continuously recorded as a finger interrogated the excised skin or the VitroSkin® surface by moving the index finger back and forth, and the friction coefficients (μ) were calculated as a ratio of the friction force and load according to:

$$\mu = \frac{F}{L} \quad (1)$$

A temperature-controlled plate was placed on top of the ForceBoard™ and the substrates were mounted on the heated plate (32 °C). Excised skin (2x5 cm^2) was mounted with hydrated filter paper underneath and pinned to the surface whereas pre-hydrated VitroSkin® (2x5 cm^2) was attached with double-adhesive tape. Before each experiment, a measurement with 10 S on untreated substrate was performed as control for changes in skin and finger. Prior to measurements, the formulations were vortexed 10 s to confirm homogenous samples and 50 μl (~20–25 mg) of each formulation was pipetted on the substrates using a M1000 positive displacement pipette (Microman®, Gilson, France). For each experiment the index finger, inclined 30°, was stroked forward and back 10 times to spread each (i.e., Canoderm®, Pickering cream, Surfactant cream and Pickering emulsions) on the substrate. The spreading area was determined by the size of the finger-tip (~1.2 cm) and spreading distance (~4 cm) corresponding to 4–5 mg cm^{-2} of formulation. The friction was measured for 30 s during application of the formulation and, 2.5, 5.5, and 11 min after without washing the index finger between measurements. Thus, any loss of the product on the finger during application was redistributed during subsequent measurements. Between each experiment, the fingers were washed and dried and then allowed an equilibrium period of approximately 3 min prior to each experiment. The finger status was controlled by measuring skin hydration. All experiments were performed in triplicates and in controlled ambient conditions (temperature = 21.5 ± 1.0 °C, relative humidity = 43.7 ± 10.3%). The friction force and the applied load were recorded with a sampling rate of 100 Hz and the applied load was maintained around 0.5 N, which has been reported to be the comfortable load when detecting tactile stimulus (Liu et al., 2008). The operators attempted to keep a constant load by following a visual indicator of the recorded load. The output data consisting of a text file of columns with time and respective forces were analyzed using MATLAB. The results such as average friction coefficients, applied load, time per stroke, change in friction coefficient with time and average forces could be summarized in an excel–file. Representative plots of the measured forces and calculated friction coefficient are shown in Fig. S2 (Supplementary information). The normalized friction coefficient was calculated by dividing the calculated friction coefficient for the applied topical formulations with the control measurement on untreated skin substrate. This means that a sample with a greater friction coefficient than 1 displays higher tactile friction than the untreated substrate.

A Corneometer (CM825, Courage Khazaka Electronic GmbH) was used to measure the skin hydration of the finger and the excised skin, prior to each experiment. A second measurement was performed on the excised skin after each experiment. The measured skin hydration is given in arbitrary units (a.u). For experiments done on VitroSkin® only the hydration of the finger was measured prior to and after each experiment.

2.5. Scanning electron microscopy

Samples were prepared by applying creams on excised skin and VitroSkin® separately by stroking the cream with the fingertip back and forth 10 times, and repeated after 2.5, 5.5 and 11 min in the same way as the tactile friction measurements. The samples were allowed to dry and the samples with dry residual films were attached to scanning electron microscopy (SEM) aluminium sample stubs using Leit adhesive carbon tape (Agar Scientific) and sputtered with gold using an Agar automatic sputter coater at 30 mA, 0.08 mbar pressure with a sputtering time of 40 s. A conducting silver bridge was painted from the top of the sample down to the stub using Electrodag 1415 conducting silver paint (Agar Scientific). SEM micrographs of excised skin and VitroSkin® with and without dried formulation residues were obtained with a scanning electron microscope (Zeiss EVO LS10) equipped with a LaB6 filament. Imaging was done in high vacuum mode using a secondary electron detector, at 15 kV accelerating voltage, 50 pA probe current and 8–10 mm working distance.

2.6. Statistical analysis

Whenever applicable, results were expressed as averages ± standard deviation, and differences were determined by one-way ANOVA with Tukey's HSD test. Statistical outliers were excluded based on two-sided Grubbs' test ($p < 0.05$).

3. Results and discussion

3.1. Influence of different untreated substrates on tactile friction

In order to compare the effects of using the two types of substrates, we first investigated the friction coefficient of the untreated substrates (no formulation applied), Fig. 1. As can be seen the friction coefficient is

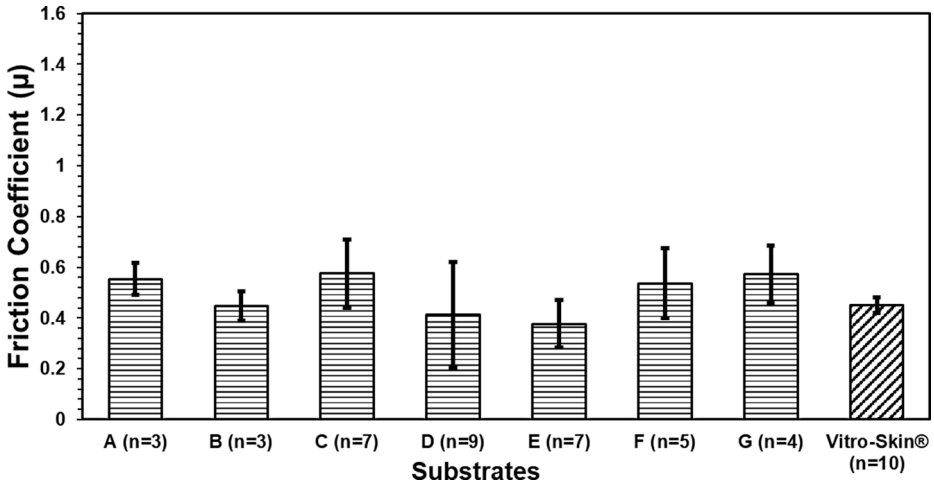

Fig. 1. The mean friction coefficient of untreated excised skin from different porcine ears A–G (horizontal stripes) and untreated VitroSkin® (diagonal stripes) measured by operator 1. Error bars show the standard deviation for n numbers of samples.

quite similar for the two different substrates and no significant difference was found ($p = 0.05$). However, the variation is as could be expected much larger for excised skin than for VitroSkin® and there is also a disparity between different porcine ears that occurs due to biological variation. To handle this variation, we propose to normalize studies on effects of topical formulations by dividing with the friction coefficient of the measurement on the pure untreated substrate and all data in the current work will be evaluated using this procedure.

3.2. *The effect of different operators on friction measurements*

In order to further evaluate the method, we also compared the results obtained by two different operators on untreated substrates, Fig. 2. The individual variation for each operator was in the same range indicating that this is a systematic difference due to the method. There is a significant difference ($p < 0.05$) in measured friction obtained by the two operators when using untreated excised skin and VitroSkin®, although the difference in absolute friction values was smaller on VitroSkin®. The skin hydration (a.u) of the fingertip was higher for operator 2 than operator 1, (37 ± 18 vs 19 ± 5 with excised skin, 30 ± 6 vs 18 ± 3 with VitroSkin®), and it is tempting to consider that the higher skin hydration for operator 2 is the cause of the increased friction coefficients. Although differences in finger hydration is often the cause of large individual differences in tactile friction (Arvidsson et al., 2017; Derler and Gerhardt, 2012), it cannot be concluded that skin hydration of the fingertip is the only cause for difference in the results obtained by the two operators. The difference can probably also be attributed to a difference in finger size and individual response in applied load by the operators (Fig. S3, supplementary information), which shows that to be able to perform comparisons with exact values of friction coefficients using this method the same operator should conduct the full study. Other studies show that repeated measurements with one operator can be representative of relative differences in tactile friction between a set of samples (Arvidsson et al., 2017). Variations in the relative humidity of the room (relative humidity $= 43.7 \pm 10.3\%$, temperature $= 21.3 \pm 0.8\,^{\circ}C$) had no systematic effect on the obtained friction coefficients for untreated substrates.

In order to investigate how repeated measurements over time affect the results, the normalized friction coefficient for untreated substrates was investigated over a period of 11 min by operator 1, Fig. 3. The difference between VitroSkin® and excised skin small when investigating untreated substrates. However, excised skin shows a small reduction ($p < 0.05$) in normalized friction coefficient over the measurement period, there there was also a tendency for reduction in skin hydration (relative change %) for most untreated skin substrates after 11 min, $27\% \pm 34\%$ ($n = 8$). Even if variation in hydration was large, this may explain the small reduction in friction coefficient. Corresponding results for VitroSkin® show no significant change in the normalized friction coefficient over the measurement period.

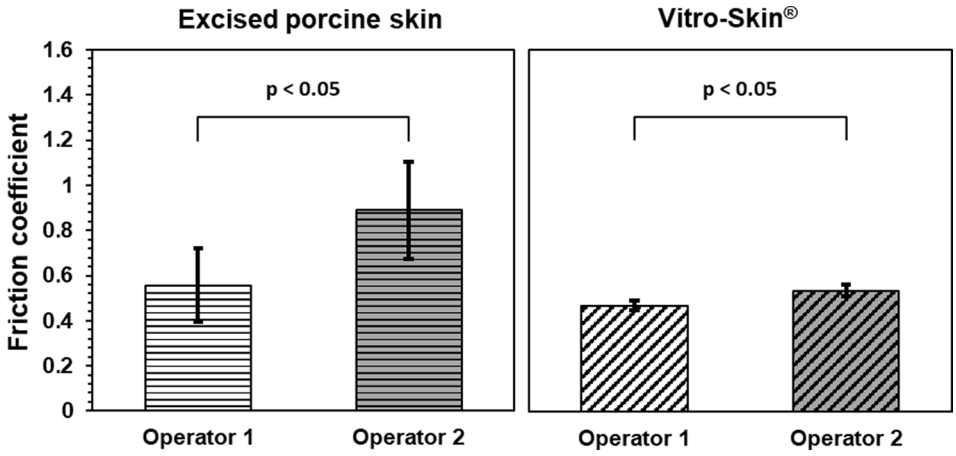

Fig. 2. Variation between operator 1 (white bars) and 2 (grey bars) when using untreated excised porcine skin (horizontal stripes, $n = 6$) and VitroSkin® (diagonal stripes, $n = 6$) for tactile friction measurements. The data is shown as mean values with error bars showing the standard deviation for n numbers of samples.

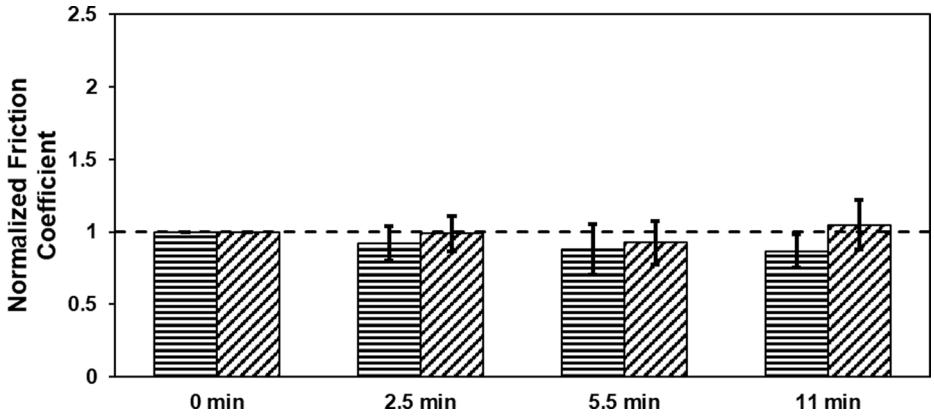

Fig. 3. Effect of time on the normalized friction coefficient for excised porcine skin (horizontal stripes, n = 8) and VitroSkin® (diagonal stripes, n = 4). Data is given as mean values with error bars showing the standard deviation for n numbers of samples.

3.3. Influence of topical creams on friction measurements on different substrates

To investigate if VitroSkin® resembles excised skin when measuring the influence of topical products on normalized friction coefficient, three different products were investigated, namely, Pickering cream, Canoderm® cream and a surfactant-based Pickering replica referred to as Surfactant cream (see Table 1 for composition). These creams have previously been shown to provide different tactile friction behaviour when measured on excised skin (Ali et al., 2022). Pickering cream and Surfactant cream have similar composition of ingredients and only differ in the type of emulsifying agents used, starch particles in Pickering cream and traditional surfactants in Surfactant cream.

During the application of a topical cream, the tactile friction is affected by the viscosity and thickness of the formed film between finger and substrate (Guest et al., 2013; Skedung et al., 2016; Tang et al., 2015). The frictional properties at this stage were thought to be related to slipperiness of the formulation (low friction = high degree of slipperiness) and the change over time was thought to reflect properties of the cream and the residual film on skin (ability to recover a normalized friction coefficient close to 1).

The difference between the previous results on excised skin (Ali et al., 2022) and the same measurements on VitroSkin® can be seen in Fig. 4. In this figure we have also added the measurements of operator 2 for Canoderm®.

The trends seen previously for these creams on excised skin was also to some extent seen for VitroSkin®, but with some notable differences. Firstly, the initial drop in normalized friction coefficient observed for Canoderm® and Surfactant cream was considerably lower on excised skin than on VitroSkin®. Secondly, while there was a small gradual increase in friction over time for Canoderm® and Surfactant cream on excised skin, on VitroSkin® the increase at 2.5 min that levelled out to close to unity for the remaining time (i.e., same as untreated substrate). The normalized friction coefficients of Pickering cream were higher than for Canoderm® and Surfactant cream, and the increase of the normalized friction coefficient was more pronounced on VitroSkin®. The variation in the results between replicates was especially distinct for Pickering cream on excised skin and therefore it was difficult to evaluate the change over time as there seems to be at least an initial increase of the normalized friction coefficient over time.

It can be concluded that the gradual changes over time seen for excised skin where not observed for VitroSkin®. There could be several reasons for this. Firstly, the topography is not identical for the two substrates as seen with electron microscopy (Fig. 5 A-B), hence the effect of spreading the creams could reduce friction more on the irregular excised skin than on the slightly smoother VitroSkin®. Secondly, oil is unlikely to be absorbed by VitroSkin® while oil is expected to be absorbed to some extent by excised skin, which could explain the larger changes over time for the latter substrate. It can especially be realized for Canoderm® and Surfactant cream on excised skin where the gradual change over time reflects the spreading of a cream leading to a reduction of the normalized friction coefficient because of hydrodynamic lubrication. Subsequent reformulation and absorption of the residual oil led to smoothening of the skin surface and a slow recovery of the normalized friction coefficient. This indicates that after the initial application, the residual film is in a mixed lubrication regime on excised skin for the remaining measurement time. On VitroSkin® however, the quick recovery in friction after spreading of Canoderm® and Surfactant cream reflects the inability of VitroSkin® to absorb the residual oil and thus no subsequent change in friction could be observed from the occlusive oil

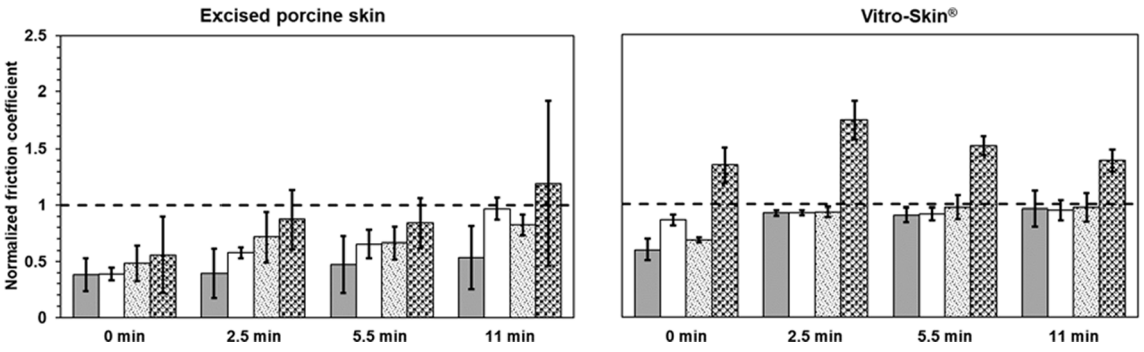

Fig. 4. Normalized friction coefficient over time for excised porcine skin and VitroSkin® at 32 °C. The tested creams were Canoderm®, Pickering cream (bar with spheres) and Surfactant cream (dotted bar) and. The test for Canoderm® was performed by operator 1 (white bar) and 2 (grey bar). All other measurements were done by operator 1. Data are shown as mean values with error bars showing standard deviation for n = 3 number of samples.

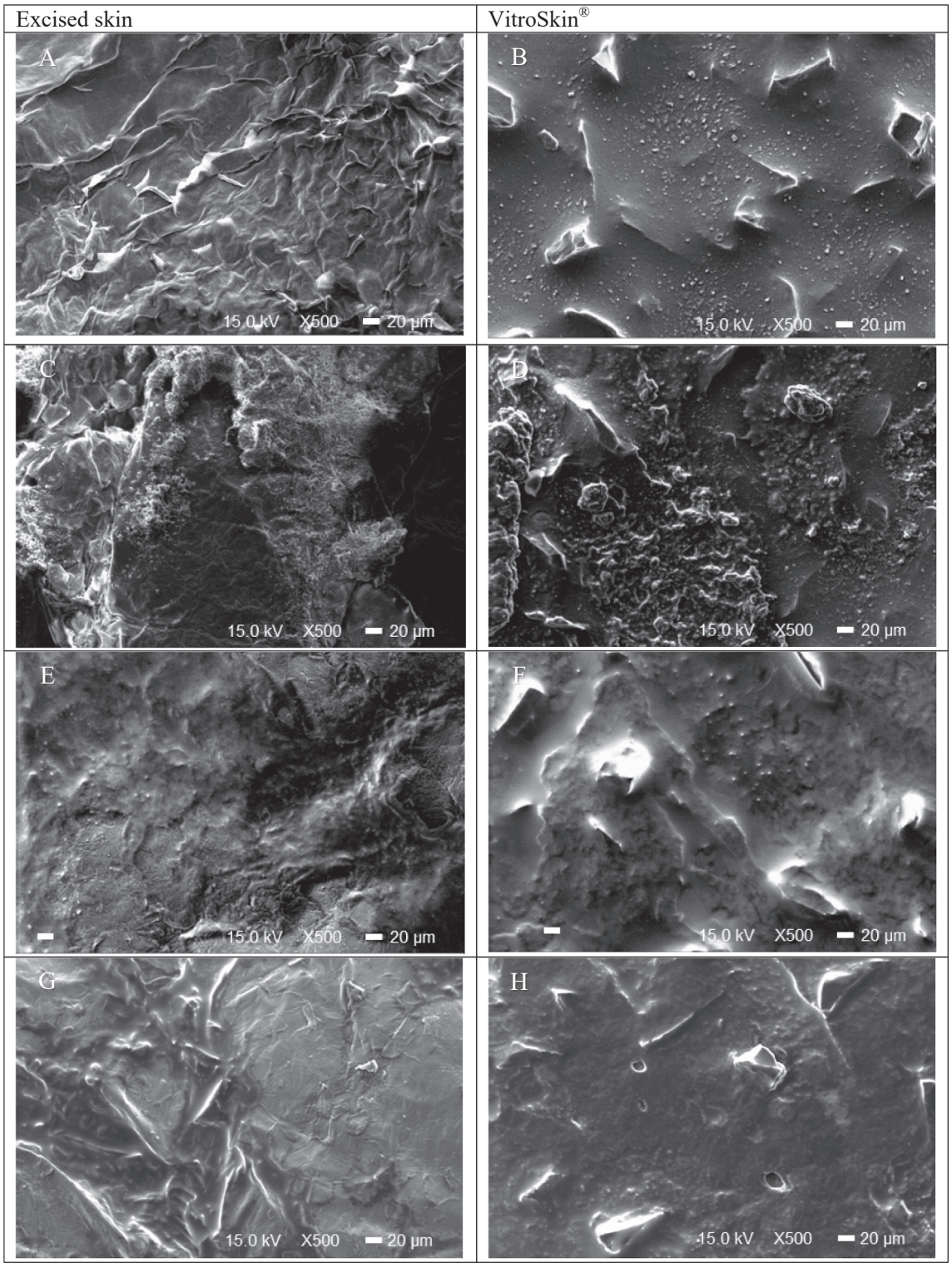

Fig. 5. Scanning electron microscopy (SEM) micrographs of dry residual films of applied creams on excised skin (left) and VitroSkin® (right). From top to bottom: Untreated substrate samples (A-B), Pickering cream (C–D), Canoderm® (E-F), surfactant-based cream (Surfactant cream) (G-H). Scalebar is 20 µm.

film. This indicates that after spreading, the thickness of the residual film is reduced exposing the peaks in VitroSkin®, and it is primarily these peaks that give rise to the friction in the boundary lubrication region (Fig. 4). The results for Canoderm® on VitroSkin® are in agreement with previous studies by Skedung et al. (Skedung et al., 2016) for a cream with similar composition, where it was also assumed that hydration resulted in further increase in friction coefficient over a longer measurement time (60 minutes). Similar observations have been made by Nacht et al. (Nacht et al., 1981) where the friction was initially reduced after application of greasy compounds, followed by gradual increase in friction over several hours. It must be kept in mind that although hydration and occluding effects might affect the tactile friction over longer time, the focus of this paper is on the perception of topical creams during and shortly after application.

The difference previously seen between the two operators for untreated substrates can now be compared to results from Canoderm® applied on excised skin and VitroSkin®. It was interesting to see if normalization of the results could reduce the differences previously seen for untreated excised skin. The difference in the results obtained by the two operators was small for excised skin in the initial measurements but over time the difference increased (Fig. 4). With VitroSkin®, there was an initial significant difference ($p < 0.05$) in results generated by the two operators, but after the first time point this difference was not significant and the operators obtained very similar normalized friction over time. We can conclude that although the operators obtained different results in tactile friction on untreated substrates, the difference between operators was rather small when topical formulations were applied. In general, one could assume that the difference in normalized friction is lower than the difference in absolute values.

It can be questioned whether changes over time as a result of reformulation and occlusion can be evaluated using VitroSkin®, whereas it could also be used to study changes over time as a result of hydration. Furthermore, the smaller variations between replicates and reproducibility of the results with VitroSkin® is beneficial from a statistical point of view to show direct differences between different types of topical creams. It can be concluded that although excised skin and VitroSkin® showed the same trends and that if one would rank the three creams the two substrates would give similar ranking, there were also considerable differences between these substrates.

3.4. Residual films at substrate surfaces

To further investigate the cause of the differences in results obtained with two substrates, we used scanning electron microscopy (Fig. 5). In line with previous studies, it can be seen that the topography and structure of untreated VitroSkin® imitates that of skin with peaks and valleys (Tang et al., 2015) while the peaks in VitroSkin® look more edgy compared to the untreated excised skin (Fig. 5 A-B). The texture of VitroSkin® becomes more elastic and soft when hydrated as indicated by images shown by Tang et al. (Tang et al., 2015). Furthermore, untreated VitroSkin® contains randomly distributed small particles in the valleys but they could be distinguished from starch particles by the shape and unique particle size of starch particles (1–3 μm). Fig. 5 (C-H) shows that for all three creams, dry formulation residues on excised skin and VitroSkin® could be clearly detected. This means that when applying the creams on the substrates with a finger in similar way as for the tactile friction measurements over a period of 11 min, there was still a detectable residue left on the substrates. Ultimately that means that during and by the end of the tactile friction measurements, the residual films of all creams on the two substrates were in the boundary/mixed lubrication regime. The Canoderm® residue (Fig. 5 E-F) displays a smoothening of the excised skin and the VitroSkin® surfaces, although the Canoderm® residue also shows some minor microstructure. The Surfactant cream residue (Fig. 5 G-H) shows more film coverage on both surfaces and exhibits similar smoothening of the surfaces as Canoderm®. The residual film of Pickering cream (Fig. 5 C-D) looks thicker than that of Canoderm® and Surfactant cream on both substrates. It is well distributed on VitroSkin® with starch and residual oil covering the surface, also creating differently sized aggregates of starch and oil locally. However, on excised skin the Pickering residue was not as well distributed with some areas covered by starch and oil, while other parts were not covered by the residual film. Furthermore, free starch could be seen on the excised skin while on VitroSkin® the starch is well distributed in the oil. The presence of starch in the residual film on VitroSkin®, and the aggregates of starch in the residual oil, could possibly increase the friction when the aggregates are rubbed against the edgy peaks. By comparing the residual films of Pickering cream (Fig. 5 C-D) to Surfactant cream (Fig. 5 G-H) it can be easily realised that the reason for the higher friction exhibited for Pickering cream is the presence of starch particles.

3.5. Influence of emollient and starch composition of Pickering emulsions

In order to further study the difference between excised skin and VitroSkin® as substrates and the mechanism behind the higher friction seen for Pickering cream, plain Pickering emulsions with different amounts of oil were investigated. The impact of the amount of oil on friction was studied by varying the triolein content in Pickering emulsions distributed on excised skin (Fig. 6), and a comparison between excised skin and VitroSkin® is shown in Fig. 7. The amount of starch added to these formulations, to ensure stabilization of emulsion droplets, is proportional to the amount of oil (300 mg starch per g oil), thus the starch content increases with increasing oil content in these emulsions.

The normalized friction coefficients of Pickering emulsions displayed in Fig. 6 differed the most during application. Lower oil content (5–10 wt%) did not induce a reduction of the friction coefficient compared to untreated skin, while higher oil content (18–26 wt%) resulted in hydrodynamic lubrication and thus a reduction in friction. Further measurements resulted in a similar or higher friction coefficient compared to untreated skin. The emulsion with 18 wt% oil significantly differed ($p < 0.05$) from the one with 10 wt% oil during the application as well as at 5.5 min. In previous studies with traditional surfactant-based emulsions it has been shown that the friction on skin decrease due to the lubrication of the applied oil layer (Savary et al., 2013). As can be seen for the Pickering emulsions this is only the case when the oil content is high and contrary to previous investigations the recovery of the friction is quite fast. In addition, Pickering creams are often described as dry and ranked low for greasiness and stickiness (Ali et al., 2022) and this is in line with a high friction coefficient. After 11 minutes, the friction coefficients of all emulsions were similar regardless of oil content. Only the emulsion with 10 wt% oil was significantly different from the three other emulsions ($p < 0.05$). When the results of the emulsions were compared with the results of the Pickering cream, the statistical analysis found no significant differences ($p = 0.05$) between the samples. This suggests that the residual film structure is similar for Pickering emulsions irrespective of oil content after a while when the oil has been rubbed into the excised skin. For Pickering emulsions with 5 wt% triolein, the change in friction coefficient is similar on excised skin and VitroSkin®. However, with higher oil content (26 wt%) the difference in friction change is much higher on VitroSkin® than on excised skin (significantly different from 5 wt%, ($p < 0.05$)). The difference in frictional behaviour observed between Pickering cream and the Pickering emulsions can be attributed to the overall structure of the cream due to addition of other excipients.

3.6. A closer look at the residual films at surfaces

The results suggest that VitroSkin® is more sensitive to presence of particles than excised skin. It can be speculated that although VitroSkin®, when hydrated, imitates the topography of excised skin, it lacks some specific features such as the wrinkles and hair follicles that are present on porcine and human skin. This difference may well account for an extra sensitivity to small particles in formulations on VitroSkin® and an initial higher tactile friction when compared to excised skin. As the water evaporates over time, the surface of VitroSkin® becomes rough and stringent resulting in higher tactile friction when the residual starch-oil film is further rubbed with the finger on this surface. Thus, on VitroSkin® the friction increases as a result of higher particle content in combination with high degree of aggregation of these particles with the residual oil. Consequently, this increase in friction is more prominent and takes over the decrease in friction normally seen for higher oil content. In comparison, excised skin can be thought to have a softer structure than VitroSkin® over time, and the presence of wrinkles and hair follicles could explain why the impact on tactile friction of different particle content in formulations is barely noticed. Consequently, particles are well distributed on the skin surface and contributing to a friction similar or slightly higher than untreated skin regardless of oil content.

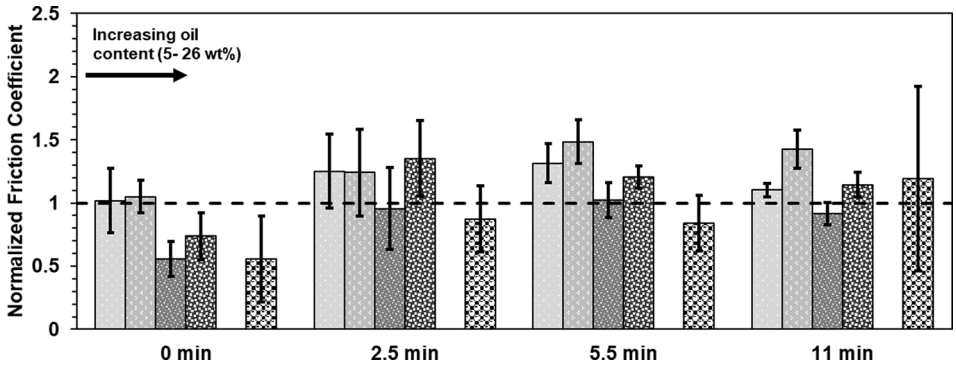

Fig. 6. Tactile friction measurements on Pickering emulsions with varying triolein oil content (and starch concentration 300 mg per g oil) on excised skin: 5 wt%, 10 wt%, 18 wt%, and 26 wt% oil (bars coloured with grey contrast from light to dark for low to high oil content, with white texture from low to high amount of starch). The test with Pickering cream with 28 wt% oil (white spheres) was also included for comparison.

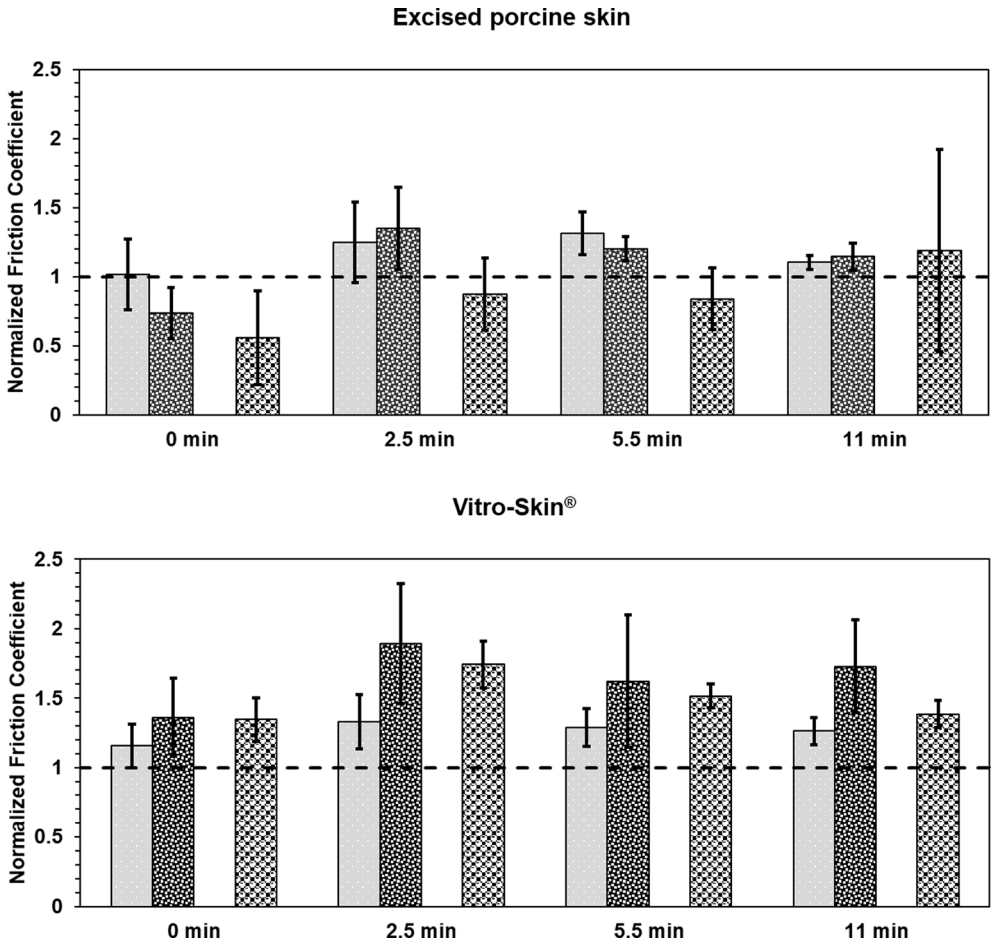

Fig. 7. Normalized friction coefficient of applied Pickering emulsions with varying triolein oil content (and starch concentration 300 mg per g oil) on excised skin and VitroSkin®: 5 wt% (light grey bar with white texture) and 26 wt% oil (black bar with white texture). The tests with Pickering cream (emulsion with other excipients) with 28 wt% oil (white spheres) are also included for comparison.

This can also be seen in the SEM image of 26 wt% oil Pickering emulsion (Fig. 8 B) where the particles seem to be well distributed over the skin surface. Furthermore, the distribution of starch particles in the residual film differs between excised skin and VitroSkin® (Fig. 8 A-B), with more freely distributed starch on excised skin, whilst being particles are more tightly packed on VitroSkin®. This could be a result of non-absorbed residual oil on VitroSkin® creating a paste-like film with the starch on the surface, while on excised skin some of the oil is absorbed leaving free starch particles on the top. This correlates well with our previously reported in vivo data (Ali et al., 2022), where a Pickering cream was perceived as non-greasy in the after–feel. For Pickering creams, it has sometimes been observed that further substantial rubbing during the application phase may cause the residual formulation to peel off from the skin as in a "snowball effect". Similar "peeling" of the residues was observed in the tactile friction measurements of Pickering cream on VitroSkin® (mainly at 2.5 minutes) but not for excised skin. Thus, it could be hypothesised that the mechanism for these phenomena could be the same. That is, that residual excipients, such as oil and/or

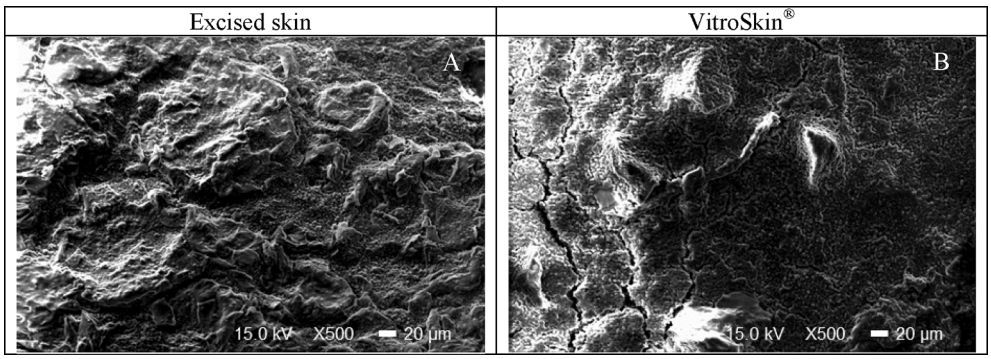

Fig. 8. Scanning electron microscopy (SEM) micrographs showing residual film of Pickering emulsion (26 wt% triolein) on excised porcine skin (A) and VitroSkin® (B).

thickener, in combination with the starch particles form aggregates, that are peeled off the skin upon further rubbing, when the oil is not absorbed fast enough into the skin. Therefore, VitroSkin® could be suitable for studying this type of phenomena, as it could possibly reflect skin types where oil absorption does not occur fast and are more prone to experience this phenomenon.

4. Conclusions

It can be concluded that there are no significant differences in obtained friction coefficient on untreated excised skin and VitroSkin® for a trained operator. The variation was, however, much larger for excised skin than for VitroSkin®. The measured friction obtained individually by the two operators differed significantly on both untreated substrates, and the variation was more substantial for excised skin than for VitroSkin®. When a topical cream was applied the difference between operators was however rather small. To study significant differences between products with controlled measurements, a single trained operator is to be preferred.

We can further conclude that when measuring on untreated substrates, the tactile friction depends on the properties of the substrate surface. Once a formulation is applied, it is the physicochemical properties of the formulation that determines the results in tactile friction.

The effect of measuring time was rather small both for untreated excised skin and VitroSkin®. On the other hand, when evaluating formulations, time effects are seen to some extent for VitroSkin®, but to much larger extent for excised skin. Nonetheless, we can conclude that excised skin and VitroSkin® showed the same trends when formulations are applied, and that if one would rank two creams towards each other the two substrates would give similar ranking.

The difference between excised skin and VitroSkin® could be attributed to surface structure differences, as demonstrated by SEM. While VitroSkin® fails to reproduce the topical properties of excised skin that affects tactile friction over time, it can be used to detect direct differences in friction between topical products. It can be a suitable substitute to avoid using animal or human skin, and to reduce the individual variation between skin substrates due to biological variation. Furthermore, it can be used to study specific features such as hydration effects, and "peeling" effects of particle-containing topical products.

The results also confirmed that there is a difference between Pickering-based formulations and surfactant-based formulations such as Surfactant cream and Canoderm®, indicating that surfactant–based creams are greasier than the Pickering cream shortly after application. It was also shown that the amount of oil only has a minor effect on the friction for Pickering emulsions. Friction is consistently high even at high amounts of oil indicating a non-greasy, and non-sticky formulation in line with previous results by Ali et al. (Ali et al., 2022). Thus, we can conclude that starch-stabilized Pickering formulations present unique characteristics allowing the development of novel surfactant-free topical formulations with specific tactile properties of the afterfeel perception.

CRediT authorship contribution statement

A. Ali: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization, Project administration. **L. Ringstad:** Conceptualization, Methodology, Investigation, Writing – review & editing. **L. Skedung:** Conceptualization, Methodology, Writing – review & editing, Formal analysis. **P. Falkman:** Investigation, Writing – review & editing. **M. Wahlgren:** Conceptualization, Methodology, Supervision, Writing – review & editing. **J. Engblom:** Conceptualization, Methodology, Supervision, Project administration, Writing – review & editing, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpharm.2022.121502.

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