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# Characterization of starch Pickering emulsions for potential applications in topical formulations

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ABSTRACT

The aim of this work has been to characterize starch based Pickering emulsions as a first step to evaluate their possible use as vehicles for topical drug delivery. A minor phase study of emulsions with high oil content has been performed. Emulsion stability against coalescence over eight weeks and after mild centrifugation treatment has been studied. The particle size, rheological properties and *in vitro* skin penetration of emulsions containing three different oils (Miglyol, paraffin and sheanut oil) was investigated. It was shown that it is possible to produce oil in water starched stabilised Pickering emulsions with oil content as high as 56%. Furthermore, this emulsions show good stability during storage over eight weeks and towards mild centrifugation. The particle size of the systems are only dependent on the ratio between oil and starch and for liquid oils the type of oil do not affect the particle size. The type of oil also affects the cosmetic and rheological properties of the creams but did not affect the transdermal diffusion in *in vitro* tests. However, it seems as if the Pickering emulsions affected the transport over the skin, as the flux was twice that of what has been previously reported for solutions.



## 1. Introduction

Topical drug delivery is used for local treatment of skin related diseases but can also be interesting for systemic delivery of drugs. The latter as topical drug delivery avoids the first pass metabolism but also that it has a high patient compliance compared to many other delivery routes. The problem with topical delivery is that the skin penetration of many drugs is low. Thus, there is a need for new topical drug formulations.

Emulsions in the form of lotions, foams and creams are the most commonly used topical delivery platforms (Lu and Gao, 2010), since emulsions have better compatibility with the skin than other delivery platforms. In this work, we investigate a new type of emulsions recently developed at the Department of Food Technology at Lund University (Dejmek et al., 2010) for the use in topical formulation. The formulations is a starch particle stabilised Pickering emulsion. Particle stabilised emulsions (Pickering emulsions) is a way to obtain surfactant free emulsions. One advantage for such a formulation strategy would be that it might be possible to avoid skin irritation that sometimes can be linked to surfactants (Welss et al., 2004). Pickering emulsions also display other advantages compared to surfactant-stabilised emulsions such as, high stability against coalescence and Ostwald ripening in a variety of formulations (Aveyard et al., 2003). The droplets are stable to coalescence because the kinetic energy of collision between droplets will be insufficient to remove the particles once adsorbed to the oil–water interface. The type of the emulsion is determined by the contact angle made by stabilising colloidal particles at the water-oil-solid contact surface (Binks, 2002). Contact angles less than 90° give rise to o/w emulsions while contact angles greater than 90° favours w/o emulsions (Miller et al., 2006). Furthermore, it has been shown that Pickering emulsion can alter the transport through skin compared to traditional emulsions (Frelichowska et al., 2009a,b). Both increased (Frelichowska et al., 2009a) and decreased (Frelichowska et al., 2009b) levels of transdermal transports have been observed as well as targeted delivery to the skin (Eskandar et al., 2009b, 2010; Ghouchi Eskandar et al., 2009). The most common particle stabilised emulsion systems tested today are based on submicron silica particles (Eskandar et al., 2009a,b, 2010; Frelichowska et al., 2009a,b; Ghouchi Eskandar et al., 2009; Simovic and Prestidge, 2007; Tan et al., 2011) and few systems are based on degradable biopolymers. In our work, we have used quinoa starch granules as the particle fraction in the emulsion. Quinoa starch, compared to most other starches, have a very small granule size of 1–2 μm and through chemical modification (octenyl succinic anhydride, OSA) starch granules can be made more hydrophobic, which gives it a higher affinity for the oil/water interface than native starch (Timgren et al., 2011).

Three different oils are used in this work: liquid paraffin, Miglyol and sheanut oil. Liquid paraffin, which is composed of

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hydrocarbons, is a common excipient in many topical creams. The other two oils used are triglycerides and were chosen to represent solid and liquid vegetable oils. Miglyol oil 812 contains medium chain triglyceride of saturated fatty acids $C_8$ and $C_{10}$. Miglyol is a liquid oil often used in cosmetics and pharmaceuticals (product information, Sasol). The third oil used was sheanut oil which consists of fats such as oleic acid (C18:1) and stearic acid (C18:0) (Davrieux et al., 2010). It has a melting point around 35–40 °C.

The active substance used as a model substance in the oil formulations was methyl salicylate. It is known to penetrate the skin and reach deeper tissue layers below the subcutaneous to provide therapeutic effects (Cross et al., 1999). Methyl salicylate like other salicylates is an anti-inflammatory and local anaesthetic. It has a molecular weight of 152 g/mol, log *P* of 2.5 (Zhang et al., 2009) and is non-charged, making it a suitable candidate for transdermal delivery.

In this work, we have focused on investigating starch stabilised emulsion with high oil content. The emulsions investigated are not fully developed commercial cream and excipients such as preservatives, colourants and perfumes have not been added. The purpose of the work has been to do a physicochemical characterization of the emulsions and to do a first preliminary investigation of skin penetration using *in vitro* skin models.

## 2. Materials and methods

### 2.1. Materials

The oils used were Miglyol 812 (Sasol, Germany, 37332-31-3, batch no: 050 223), paraffin (Merck, Germany, 1.07174, batch no: K40901874049) and sheanut oil (Karlshamn, Sweden, 940915, batch no: LL963). The starch used was extracted from quinoa grains (Biofood, Sweden, 06-2009, batch no: 07-2009) and chemical modified by octenyl succinic anhydride (OSA) to a substitution degree of 1.8%. Methyl salicylate (Fluka, 84332, batch no: BCBB8062) was obtained from Sigma-Aldrich (Stockholm, Sweden). All other chemicals were of PA quality and Milli-q water was used in all experiments.

### 2.2. Preparation of emulsions

The water phase (5 mM phosphate buffer with 0.2 M NaCl, pH 7) containing the starch granules was mixed with the oil phase with a vortex mixer (VM20, UK) and then emulsified using a high shear mixer (Ystral D-79282, Germany) at a speed of 22,000 rpm for 1 min. Preliminary test formulations using Miglyol oil were prepared with varied amounts of buffer, starch and oil in 14 ml glass test tubes at room temperature, see Tables 1 and 2. Emulsions with paraffin and sheanut oil were produced using 56% oil and 214 mg starch/ml oil. Sheanut oil was heated to 45 °C in water bath for 1 h prior to emulsification to be in a liquid state during mixing. For the diffusion studies, methyl salicylate was dissolved in the oil phase before subsequent emulsification. Emulsions were prepared in triplicate for each condition.

### 2.3. Phase studies and stability studies

The emulsions where inspected visually and a drop of Sudan Red 26 was added to the emulsion to detect whether or not the oil phase was continuous. The emulsions where also investigated after 1 h settling time for creaming and sedimentation. The emulsions where inspected in a microscope and the droplet size determined using laser diffraction as described below. Some of the emulsions were sealed and stored at 25 °C in 14 ml glass test tubes for 8 weeks. The creaming and sedimentation of the emulsion as well as their rheological properties where investigated on the day of preparation and after 8 weeks storage. The formulations were examined regarding consistency and appearance of phase separation, droplet size and rheological properties. To further investigate the stability of the emulsions, some emulsions were centrifuged (Beckman Coulter, Allegra® X-15R, L 284). The relative centrifugal field (RCF) was 1000 g and the duration of centrifugation was 81 min at a temperature of 21 °C.

**Table 1**
Phase study using Miglyol oil: effect on phase behaviour and particle size (average and standard deviation of two samples measured three times).

| Miglyol oil [%] | Starch [mg/ml oil] | Visual observation | $d_{4,3}$ [μm] | $d_{3,2}$ [μm] |
|---|---|---|---|---|
| 27[a] | 200 | o/w – creaming | 36 ± 9 | 32 ± 7 |
| 41[b] | 214 | o/w – no creaming | 33 ± 2 | 27 ± 3 |
| 41[a] | 200 | o/w – no creaming | 32 ± 2 | 29 ± 4 |
| 41[a] | 130 | o/w – some creaming | 52 ± 7 | 50 ± 6 |
| 41[a] | 65 | o/w – creaming | 65 ± 4 | 50 ± 3 |
| 56[b,c] | 214 | o/w – no creaming | 43 ± 3 | 27 ± 5 |
| 56[a] | 150 | o/w – no creaming | 44 ± 1 | 29 ± 3 |
| 56[b] | 97.2 | o/w – no creaming | 52 ± 2 | 45 ± 5 |
| 56[a] | 97 | o/w – no creaming | 61 ± 5 | 42 ± 17 |
| 56[a] | 49 | o/w – creaming free oil | 74 ± 7 | 57 ± 3 |
| 70[a] | 120 | o/w – no creaming, oil on top | 59 ± 14 | 13 ± 3 |
| 70[a] | 77 | o/w – oil on top | 64 ± 8 | 15 ± 1 |
| 70[a] | 39 | No emulsion | – | – |
| 84[a] | 64 | No emulsion | – | – |

[a] Preliminary test series.
[b] New formulations based on the preliminary test.
[c] Measurements of 5 samples.

### 2.4. Characterization methods

The emulsions where investigated using an optical microscope (Olympus BX50, Japan) which was equipped with a video camera. The emulsions were diluted 5 times with buffer and one drop was added on a glass plate without cover glass for microscopic observation.

Size distributions of the emulsions were determined by using a laser diffraction particle analyser (Coulter LS 130, Beckman Coulter, England). The *d*[4,3] and *d*[3,2] values were calculated. This as the volume weighted mean of the particle *d*[4,3] is important for factors related to structure in the cream such as space fill and that surface area weighted mean *d*[3,2] is important for issues related to the interfacial area, such as transport.

The rheological measurements were performed in a rheometer (Malvern Kinexus, England). Emulsions were analysed at two temperatures, 25 °C and 32 °C, using concentric cylinders. The rheological properties of the emulsions were observed immediately after sample preparation and after 8 weeks storage. Oscillatory tests were performed in the frequency range of 0.1–10 Hz at a strain of 1 mPa. The storage ($G'$) and loss ($G''$) moduli, phase angle ($\delta$), and viscosity ($\eta$) were measured. Furthermore, a linear stress ramp in

**Table 2**
Characterization of Pickering emulsions containing 56% oil and 214 mg starch/ml oil, particle size (mean and std for three samples measured three times) effect of storage and mild centrifugation (sed).

| Dispersed phase type | Miglyol | Paraffin | Sheanut oil |
|---|---|---|---|
| Week 1, $d_{4,3}$ [μm][**] | 43 ± 3 | 48 ± 2 | 73 ± 17 |
| $d_{4,3}$ [μm], sed | 48 ± 7 | 58 ± 11 | 76 ± 19 |
| Week 1, $d_{4,3}$ [μm][*] | 47 ± 8 | 58 ± 13 | 201 ± 69 |
| Week 8, $d_{4,3}$ [μm][*] | 48 ± 3 | 55.5 ± 6 | 224 ± 36 |
| Week 8 (fridge), $d_{4,3}$ [μm][*] | 51 ± 13 | 67 ± 14 | 128 ± 43 |

[*] Represent results from the second preparation of emulsions.
[**] Mean and std for 5 samples.

the range 0.1–10 Pa was performed and the viscosity was measured. The peak in these measurements was determined and both the shear viscosity and the shear stress at this point was ascertained.

### 2.5. Sensory analysis

A sensory analysis was performed using an in house panel of nine participants. The panel was asked to scale characteristics of the emulsions and compare them with each other. Sensory parameters were evaluated by a small amount of each formulation applied between the fingertips and rubbed into the skin. Samples were coded and provided in randomized order. A comparison was made with regard to the following attributes on a scale from 5 (very/high) to 1 (little/low):

- Visual appearance of the formulation
- Feel of the cream (thick, sticky, slippery, watery)
- Skin feel during absorption (force needed for spreading, permeability)
- Skin feel/appearance after absorption (glossy, residues).

### 2.6. Flow-through cell diffusion studies

Skin diffusion measurement was performed according to the method described by Bjorklund et al. (2010). The study was performed in a flow cell by monitoring the transport of methyl salicylate from three different topical formulations across pig skin.

A pig's ear (Ugglarps AB, Sweden) was provided from the Malmö University for the flow-through cell diffusions studies. The skin was cleaned with tap water and the hair was cut with a trimmer. Finally, a membrane with a thickness of 500 μm was obtained by using a dermatome (TCM 300 BL, Nouvag). Before use, the membranes were washed with phosphate buffer.

The diffusion experiments were performed in seven-chamber diffusion cells. The flow-through cells were inserted into a heater block so that the temperature could be controlled. The donor and receptor phase were separated by a membrane with a diffusion area of 0.64 $cm^2$ (9 mm Ø). A water bath with the temperature set at 32 °C was connected to the system. The buffer (0.1 M phosphate buffer pH 6.8 as the receptor phase) was degassed under heating (40 °C) to avoid air bubbles before it was pumped through the system at a flow rate of 2 ml/h.

About 1 g of the emulsions (donor phase) were spread uniformly on the membranes. The study was carried out in occlusive conditions by covering the cells with parafilm to avoid evaporation. Samples were collected every 2 h during 12 h and were analysed using a spectrophotometer (Varian Carry 50Bio) at the detection wavelength for methyl salicylate (302 nm) (Bjorklund et al., 2010). All emulsions, at least in duplicate and in the case of paraffin in some cases as triplicate, were tested at the same time. Each experiment was run in three independent replicates giving a total of six too eight measurements for which the mean value and standard deviation was calculated.

## 3. Results and discussion

### 3.1. Phase studies

In the first series of experiments, a number of emulsions were made which differed in oil content and in starch/oil ratio. All formulations were analysed using visual observations and the droplet sizes were measured (Tables 1 and 2).

The eleven preliminary test emulsions had oil ratios in the range of 27–84% and the amount of starch varied from 39 to 200 mg starch/ml oil. In most of the systems, o/w emulsions were observed

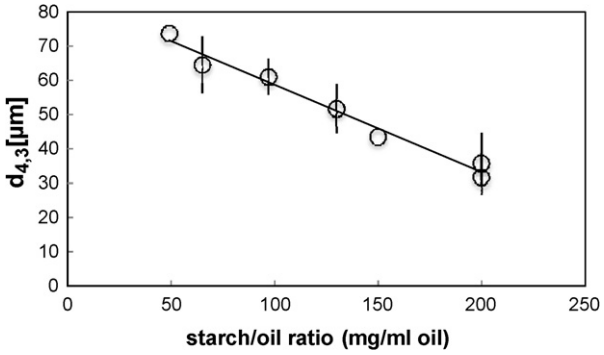


**Fig. 1.** The effect of starch/oil ratio on the droplet size ($d_{4,3}$) for emulsions containing between 24 and 56% Miglyol oil.

and none of the investigated samples showed water in oil emulsion, see Table 1 for visual observation for each system. At oil concentrations above 70% it was not possible to form a stable emulsion at the conditions used here and as seen in Table 1 emulsion with more than 41% oil and/or 49 mg starch/ml oil gave non creaming systems, otherwise creaming was observed after 1 h. At oil concentrations up to 56%, the average droplet size of the emulsions decreased when the amount of starch per ml oil increased (Fig. 1) and this decrease was independent of the amount of oil in the sample. This is in line with previous investigations where a higher amount of starch allowed the stabilisation of larger surface area (Rayner et al., 2012) The increase in starch to oil ratio did not only affect the droplet size but it also gave a more narrow droplet size distribution (Fig. 2). However, for 70% of oil the effect of increasing starch concentration could not be seen, indicating that either the emulsification method used was not sufficient or that the oil ratio was in fact too high to create stable emulsions. It was also obvious from visual inspection that when using 70% oil non-emulsified oil was observed in the test tubes.

The range of formulation conditions that gave emulsions with homogenous white-creamy appearance where investigated further. New formulations where made in this range, see Table 1 and the stability of formulations was investigated using sedimentation centrifugation. There were only small changes in droplet size induced by centrifugation. The largest changes in droplet size were

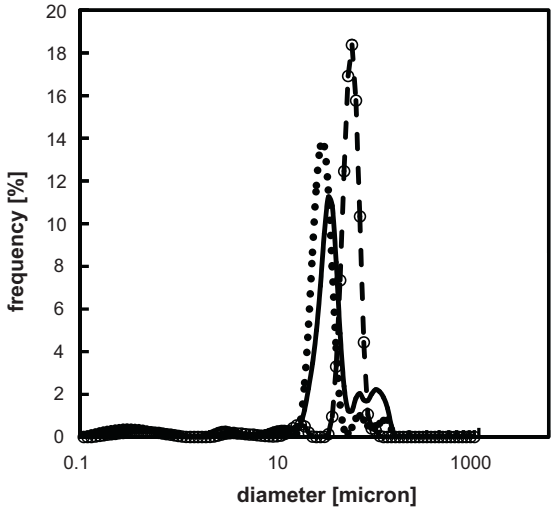


**Fig. 2.** Effect of starch/oil ratio on particle size distribution ($d_{4,3}$) in Miglyol/quinoa starch/water emulsions; circles and dotted line: 56% oil and 97.2 mg starch/ml oil, solid line 56% oil and 214 mg starch/ml oil and dotted line 41% oil and 214 mg starch/ml oil.

**Table 3**
Rheological characteristic of the creams; effect of measuring temperature and storage for eight weeks.

| | | $G'$ (Pa) | $G''$ (Pa) | Phase angle (°) | Yield stress (Pa) | Viscosity at yield (Pa s) |
|---|---|---|---|---|---|---|
| Miglyol | 25 °C | 1461 | 126.6 | 4.9 | 32 | 7174 |
| | 32 °C | 1390 | 108.2 | 4.5 | 36 | 2950 |
| | 32 °C stored | 1018 | 63.26 | 3.6 | 24 | 1048 |
| Paraffin | 25 °C | 1491 | 128.7 | 5 | 36 | 2979 |
| | 32 °C | 1799 | 140.6 | 4.5 | 49 | 5290 |
| | 32 °C stored | 1087 | 95.65 | 5 | 34 | 3151 |
| Sheanut oil | 25 °C | 29,000 | 6873 | 13 | 85 | 17,230 |
| | 32 °C | 18,000 | 7385 | 22 | 49 | 5290 |
| | 32 °C stored | 26,000 | 6501 | 14 | 57 | 9037 |

seen for the 56% oil and 92 mg starch sample where there was an increase in $d_{3,4}$ of less 10 μm. This emulsion did also show some creaming after centrifugation. The least affected emulsion were the ones containing 56% oil and 214 mg starch/ml oil, which did not show any significant change in droplet size and was homogenous after centrifugation. This system, according to our calculations will provide droplets that have approximately the same density as the continuous phase at room temperature. This density matching will provide oil droplets that buoyancy neutral, *i.e.* neither floats nor sinks. This should increase the stability of the system towards creaming.

The system containing 214 mg/ml of starch and 56% oil was therefore selected for further investigations concerning droplet size, rheological properties, stability, sensory properties and release of active substance for emulsions containing the three different oils: Miglyol, paraffin and sheanut oil.

The main results with respect to physical properties are presented in Tables 2 and 3. All three types of oils gave emulsions that initially were homogenous without creaming or sedimentation at a visual inspection. While Miglyol and paraffin gave creams with similar properties, both regarding rheological properties and droplet size, the solid fat (sheanut oil) differed having a higher mean droplet size, and a much higher viscosity and yield stress. The microscopy images of the emulsions (Fig. 3) could explain these differences. While the Miglyol and paraffin emulsions had spherical oil droplets, the sheanut oil formed droplets that were not completely spherical and that seemed to have a higher degree of aggregation. The difference was even more obvious when looking at the droplet size distribution (Fig. 4). Paraffin and Miglyol oil emulsions had one dominating peak with close to normal distribution, and just a small fraction of the droplets at larger sizes indicative of aggregated droplets. Sheanut oil emulsions on the other hand had a larger variation in the mean droplet size (Table 2) and a droplet distribution that did not comply with the emulsions expected normal distribution but instead had a quite skewed peak appearance with one fraction of droplets similar in size to the other samples but with a large tail towards larger droplets (Fig. 4). This would, most likely, be caused by the rapid cooling of sheanut oil during emulsification leading to solidification, which would cause two populations of droplets. One population including droplets formed prior to solidification and thereby comparable to the liquid oil emulsions and a population of droplets produced from solid or semisolid fat causing a broader size distribution. The latter droplets will to a large extent affect the properties of the sheanut oil cream.

After sedimentation, centrifugation a slight separation was seen for the Miglyol and paraffin emulsions indicating that the oil droplets had sedimented to some extent. No sedimentation or creaming was visible for the sheanut oil. This could be due the fact that this emulsion had a much higher viscosity (Table 3). It should be pointed out that creaming and sedimentation could not be observed for any of the creams after 8 weeks of storage. The sedimentation centrifugation did not to any significant degree change the mean $d_{4,3}$ value. As can be seen in Fig. 4 the droplet distributions show a slight increase in the larger drops (the reader should be aware that the volume mean, and not number mean, particle size is plotted and that this over emphasizes the larger droplets in the distribution). Again, the sheanut oil seemed to display higher amounts of large droplets or aggregates. For these samples, the rheological properties were investigated. Since the same samples could not be used for both rheological characterisation and droplet size analysis, a second set of samples where prepared and the droplet size analysed after 1 week and after 8 weeks storage in room temperature and in refrigerator. The results are presented in Table 2. As can be seen Miglyol and paraffin oil emulsions had the same droplet size as previously and the mean droplet sizes were not affected by storage. The second set of sheanut oil emulsions had a much larger droplet size than previous samples, which could be due to aggregation of droplets. This indicated that the production procedure for sheanut oil was not optimal, probably due to too fast cooling of the oil during emulsification leading to fast solidification and uneven droplet sizes. However, there is no evidence that the sheanut oil to any larger extent changes its droplet size during storage.

### 3.2. Texture and cosmetic properties of the creams

In order to evaluate cosmetic properties of the creams a simple sensory test with a small panel of nine participants was performed (Table 4). In the sensory test four basic characteristics were investigated by the panellist, *i.e.* visual appearance, feel of cream, and skin feel during and after application.

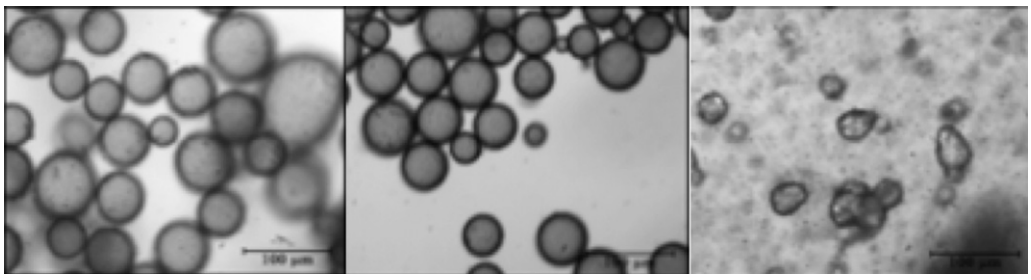

**Fig. 3.** Microscopic images of the emulsions from right to left: emulsion with Miglyol oil, emulsion with paraffin oil and emulsion with sheanut oil.

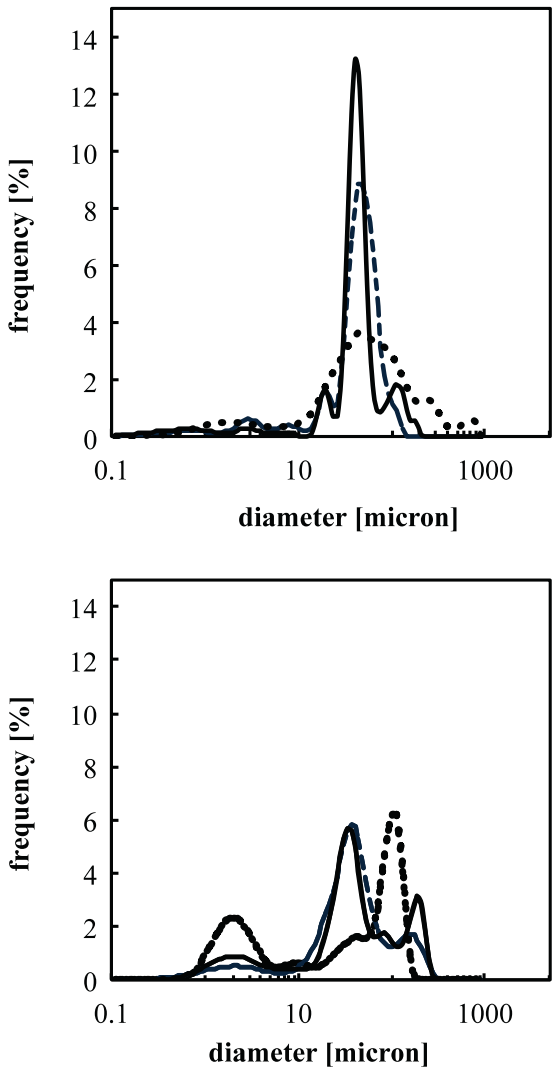


**Fig. 4.** Particle size distribution ($d_{4,3}$) for 56% oil and 214 mg starch/ml oil emulsions containing paraffin oil (solid line), Miglyol (doted line - - -) and Sheanut oil (doted line ····). Top before centrifugation bottom after centrifugation.

Even with this rather small panel, some important trends were observed. Firstly, the liquid oil creams were mainly considered to have more similar properties than the one produced from sheanut oil and this was especially obvious for parameters related to rheological properties of the cream such as thickness and force of spreading. This was in line with the measured rheological properties of the creams (Table 3). The Miglyol and the paraffin were considered to be watery indicating that the emulsion in itself was not enough to produce a cosmetically acceptable product. Only one panellist found the creams to have very low permeability into the skin and the sheanut oil was considered by most panellists to be very permeable. The panellists noted that there were some residues on the skin after application of the creams. However, this was a residue associated with the oil and not with the starch. Thus, the starch particles used for stabilisation did not give any residues on the skin that reduced its cosmetic appearance.

All the three tested creams had similar rheological behaviour although the sheanut oil emulsion was stiffer. Fig. 5 shows oscillating measurements of Miglyol oil emulsion as an example, and Fig. 6 shows yield stress measurements of all three types of samples. In the oscillating frequency sweep only small changes were detected in $G'$, $G'$ and the phase angle for all the frequencies tested. All creams tested had typical elastic behaviour since $G'$ was higher

**Table 4**
Individual results of the sensory test. The first number represents the panelists' opinion of the creams where 5 is very and 1 is that little or not at al. The number in brackets represents the number of panelists, which in total were 9.

| Properties | Miglyol | Paraffin | Sheanut oil |
|---|---|---|---|
| Thick | **1** (5) | **2** (7) | **5** (9) |
| | 3 (3) | 4 (1) | |
| | 2 (1) | 1 (1) | |
| Slippery | **5** (5) | **4** (7) | **1** (6) |
| | 3 (2) | 1 (1) | 2 (2) |
| | 4 (1) | 2 (1) | 3 (1) |
| Sticky | **2** (6) | **3** (3) | **5** (6) |
| | 1 (2) | **2** (3) | 4 (2) |
| | 3 (1) | **1** (3) | 3 (1) |
| Watery | **5** (7) | **4** (7) | **1** (6) |
| | 4 (1) | 5 (1) | 2 (3) |
| | 3 (1) | 3 (1) | |
| Force | **1** (6) | **2** (7) | **5** (9) |
| | 2 (2) | 3 (2) | |
| | 3 (1) | | |
| Permeability | **3** (5) | **3** (3) | **5** (4) |
| | 2 (2) | 2 (3) | 4 (2) |
| | 4 (1) | 5 (2) | 2 (2) |
| | 1 (1) | 4 (1) | 1 (1) |
| Glossy | **2** (4) | **3** (4) | **4** (3) |
| | 4 (3) | 5 (2) | 1 (3) |
| | 3 (1) | 2 (2) | 3 (2) |
| | 1 (1) | 4 (1) | 5 (1) |
| Residues | **3** (3) | **2** (3) | **5** (3) |
| | 1 (3) | 4 (2) | **2** (3) |
| | 2 (1) | 3 (2) | 4 (2) |
| | 4 (1) | 5 (1) | 3 (1) |
| | 5 (1) | 1 (1) | |

than $G''$ in the whole interval and consequently, the phase angle is low Table 3. This indicated that the emulsion drops formed a three-dimensional particle network. This gel network had a yield stress of 32–36 Pa for the fluid liquid oil emulsions and 86 Pa for the sheanut oil emulsion. This is in line with the fact that the sensory panel found the sheanut oil to be thicker and stiffer, requiring more force during spreading. It has been shown that Pickering emulsions give three-dimensional networks also at low concentrations of oil and that the particles used help to build up this network (Lee et al., 2012). Lee et al. explained this as percolating network of colloidal particles that works as scaffolds between the oil droplets. Although

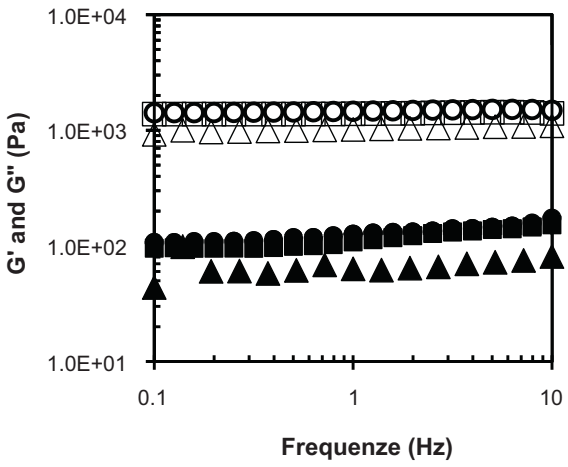


**Fig. 5.** Frequency sweep for 56% oil and 214 mg starch/ml oil emulsions. Elastic and viscous modulus, for emulsion containing Miglyol oil measured at 25 °C, circles: 32 °C, squares: stored for 8 weeks at room temperature measured at 32 °C, triangles: $G''$ filled: $G'$ opened.

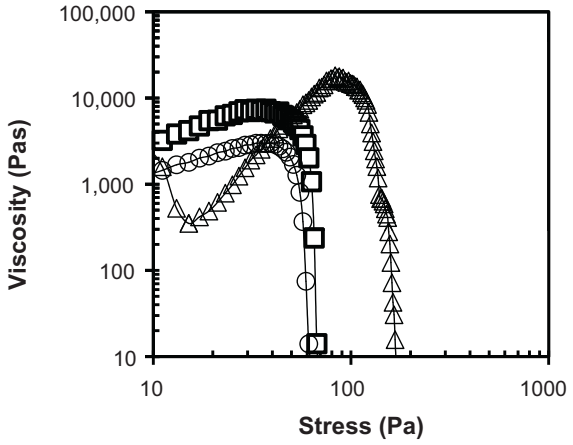


**Fig. 6.** Stress sweep for 56% oil and 214 mg starch/ml oil emulsions containing paraffin oil (circles), Miglyol (squares) and sheanut oil (triangles) measurements performed at 25 °C.

our gels had a high oil concentration the very strong and consistent gel character could be explained by similar stabilisation factors. The yield stress measurements show initially an increase in viscosity with increasing stress. This has also been seen for other emulsion systems (Brummer and Godersky, 1999) and could be related to an initial rearrangement of the particle network leading to a stronger network that at the higher shear rates are broken.

The rheological properties of the creams where also tested at room temperature and at 32 °C (skin temperature) before and after 8 weeks storage (Table 3). Only minor changes in rheological properties were seen due to the temperature difference, with the exception of the yield stress for sheanut oil cream that was reduced by more than 40% when the temperature was changed. The fact that the sheanut oil formulation was most affected by temperature was logic as the melting point of the oil was close to the interval investigated. The rheological properties at 32 °C were also investigated for creams stored for 8 weeks. Considering that these creams were far from optimized products, for example not being produced to minimize microbiological contaminations and with no preservatives added, it is promising that the rheological properties did not change to a larger extent during the storage time (Table 3). These small changes were also in line with the results from the droplet size measurements.

### 3.3. *In vitro* skin penetration

The *in vitro* skin penetration of all three formulations where investigated (Fig. 7). The steady state flux was around 8 μg/(cm$^2$ h)

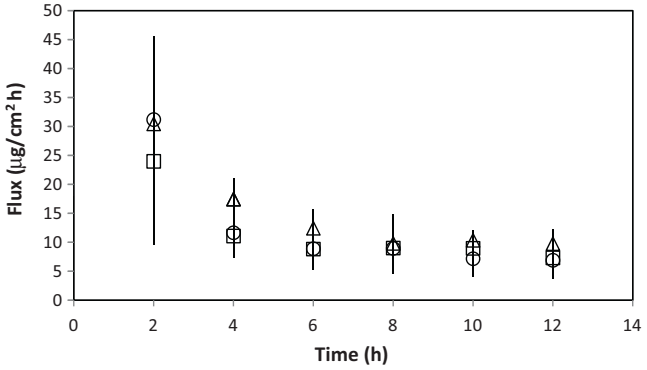


**Fig. 7.** *In vitro* skin penetration of methyl salicylate through pig skin at 32 °C, of 55% oil starch Pickering emulsions; paraffin oil (circles), Miglyol (squares) and sheanut oil (triangles).

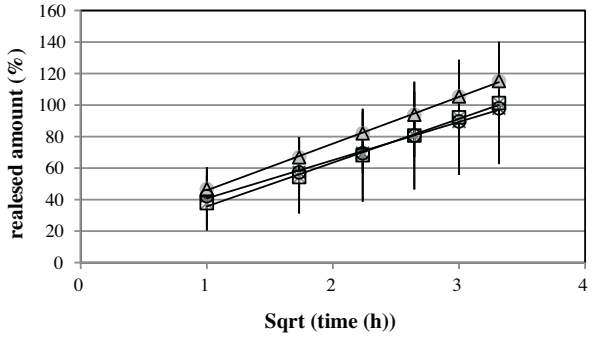


**Fig. 8.** Cumulative release profile of methyl salicylate through pig skin at 32 °C, of 55% oil starch Pickering emulsions; paraffin oil (circles), Miglyol (squares) and sheanut oil (triangles).

for all creams. This flux is nearly two times higher than what have previous been observed in a similar experimental set up using buffer solutions of the same concentration of methyl salicylate. For the buffer experiments the flux where 4.2 ± 0.7 μg/(cm$^2$ h) (Bjorklund et al., 2010). This indicates that that the presence of the emulsion system increased the penetration over the skin. The factors that affect transdermal transport from emulsions are, as pointed out by Otto et al. (2009), not yet fully understood since the formulation can alter both the properties of the skin and affect the activity of a substance. Pickering emulsions have previously been seen to increase the penetration of Caffeine compared to traditional formulations due to better adhesion of the droplets to the surface and penetration of the particles into the skin (Frelichowska et al., 2009a). It could be that similar mechanisms affect the transport in our case although further studies are needed to verify the results.

Initially the penetration flux also decreased with time. Welin-Berger et al. (2001) has shown that this could be due to depletion of the oil droplets closest to the skin. In high viscosity systems as ours the diffusion of oil droplets are hindered and thus there will be a concentration gradient and a steady state region formed. However, it could also be an indication that transport from the emulsion droplets to the water phase is more rate limiting than the transport over the skin. An indication for his could be that the cumulative release, see Fig. 8, is after a first burst linear to the square root of time which is indicative of diffusion limited transport.

In a system as this one, the rate limiting step for transport could be either in the penetration of the stratum corneum or in the transport from oil phase to the water phase in the latter case the surface to volume ratio will effect the release of active substance. This is of course especially important if the final rate limiting step is the transport from the oil phase to the water phase. In that case, the properties of the interfacial region might also affect the transport. In our case it has been observed in unpublished studies that the starch particles adsorb primarily as a monolayer although some small aggregates of starch might also occasionally adhere to the primary monolayer. Since there were no differences in *in vitro* skin penetration between the three oils used it was concluded that the system as such provided this rather high penetration. Therefore, similarities in terms of for example oil droplet size and the particles used for stabilisation were more important than the rheological properties and the individual properties of these rather dissimilar oils for the use of starch Pickering emulsions as a topical drug delivery system.

## 4. Conclusions

In this work, we have shown that it was possible to produce oil in water starch stabilised Pickering emulsions with oil content as

high as 56%. Furthermore, these emulsions showed high stability during storage over 8 weeks, both to droplet size changes, changes in rheological properties and towards creaming or sedimentation.

The droplet sizes of the systems studied were only dependent on the ratio between oil and starch, not on the oil ratio as such. Furthermore, for liquid oils the type of oil did not seem to affect the droplet size. In the case of sheanut oil, there were some difference in droplet size compared to the liquid oils but this could be due to that, the solidification of the oil during production might affect the droplet size. The type of oil also affected the cosmetic and rheological properties of the creams but did not affect the transdermal diffusion in *in vitro* tests. The transport over the skin seemed to be affected by the Pickering emulsion formulation as the flux was twice that of what has been previously reported for solutions.

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