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Topical Pickering emulsion versus classical excipients: a study of the residual film on the human skin

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Abstract

The interest in Pickering emulsions is based on the possibility of replacing classical emulsifiers with solid particles. These emulsions are very attractive in the pharmaceutical field for their stability virtues and as a vehicle to deliver active ingredients. The study aimed to analyze the properties of the residual film of the Pickering emulsions on the human skin compared to conventional systems.

For this project, three types of solid particles were used: titanium dioxide, zinc oxide and silicon dioxide. All of them are capable of stabilizing the oil/water interface and thus forming totally emulsified systems. To create an emulsion of reference, a classical surfactant was used as an excipient. Complementary systems containing both particles and the emulsifier were also analyzed. Then, a combined approach between physicochemical and biometrological *in vivo* analysis was employed.

The study proved that Pickering emulsions stabilized by the metal oxides were distinct from the reference emulsion in terms of droplet sizes and organization, rheological and textural responses. Consequently, it impacted the properties of the residual film once the product was applied to the skin. The particle-stabilized emulsions formed a hydrophobic film counter to conventional excipients.

Also, the Friction parameter (or the roughness of the film) was directly linked to the quantity of the particles used in the formulation and their perception on the skin surface. The use of the particles blurs the glossy effect of the oil phase. Finally, it was observed that the appearance of the residual film was impacted by the type of the particle, namely TiO_2 and ZnO particles.

Keywords

Pickering emulsion

Physical UV filters

Topical

In vivo evaluation

Particle stabilization

Mixed emulsifier systems

1 Introduction

The interest in Pickering emulsions lies in the possibility of replacing conventional emulsifiers with solid particles (Binks, 2006; Pickering, 1907) by forming emulsions with a great stability potential towards coalescence and Ostwald ripening (Albert et al., 2019; Binks, 2002; Kargar et al., 2011). To study the ability of the solid particles to stabilize the interface of two non-miscible liquids, an important number of solid particles, of different characteristics, were described in the literature: chitosan (Asfour et al., 2017; Wang and Heuzey, 2016), cyclodextrin (Yang et al., 2017), starch (Marto et al., 2018; Rayner et al., 2014), iron oxides (Udoetok et al., 2016), titanium dioxide (Stiller et al., 2004), silica (Arditty et al., 2003; Binks and Yin, 2016; Frelichowska et al., 2009a; Torres et al., 2007), etc.

Some of these systems are showing great potential in pharmaceutics and dermocosmetics (Marku et al., 2012; Marto et al., 2015), namely for all-*trans*-retinol (Frelichowska et al., 2009a; Simovic et al., 2011) or caffeine (Frelichowska et al., 2009b) skin delivery through topical application. For example, the systems with silica particles are mainly focused on the emulsion's capacity to play the role of the vehicles for the active ingredients and their diffusion in the *Stratum Corneum* (Frelichowska et al., 2013, 2009a, 2009b). The first work in this field was performed by Frelichowska *et al.* (Frelichowska et al., 2009b) demonstrating the first example of W/O silica particle-based Pickering emulsions for the transdermal delivery of caffeine. The better penetration of the actives was linked to improved adhesion of the Pickering emulsions to the skin surface coupled with a deep skin penetration of the stabilising silica nanoparticles, leading to enhanced drug release.

Harman *et al.* (Harman et al., 2019) discussed the recent developments in Pickering emulsions for biomedical applications for wound healing (Asfour et al., 2017) or for sunscreens (Binks et al., 2016; Marto et al., 2016b) application, where the emulsifying particles can be physical UV filters in combination with an encapsulated active agent, such as melatonin (Marto et al., 2016a). The authors also gave an important number of examples, proving that the choice of emulsifier and oil in the formulation can affect the permeability of the Pickering emulsions, their depth of penetration within the skin, and accumulation of particles, therefore affecting drug efficacy (Hu et al., 2018; Leclercq and Nardello-Rataj, 2016; Wang et al., 2017).

It is also important to question the use of solid particles on the microscopic and macroscopic properties of emulsions. The stabilization of the oil/water interface by the particles alone or combined with a classical surfactant compared to a conventional system changes the emulsion organization with a further impact on its textural properties (Terescenco et al., 2019). Furthermore, this impact strongly affects the spreading properties of the system, pointing to the interdependency between the use of the metal oxides and the applicative properties of the emulsions containing them. These texture properties are essential to ensure ease of application and an adequate distribution of the product on the skin.

The relationship between sensorial and physical characteristics of topical creams was recently studied by Ali *et al.* (A Ali et al., 2022). The authors discuss the prediction of some sensorial attributes by means of rheology and frictional measurement. However, the study is based on only one type of starch particles, leaving the questioning on the behaviour of other Pickering-forming particles.

Consequently, in addition to information about the diffusion of the actives through the skin, it is also essential to investigate the interaction between the Pickering emulsion and the skin surface depending on the emulsion composition and the particle type used for the emulsion stabilisation.

To describe the residual film of the Pickering systems, one can take an example of the classical emulsions. However, even for the emulsions containing a usual surfactant, few studies deal with the “after application” phase and the fate of the product on the skin (Eudier et al., 2019a; Savary et al., 2019). Different instrumental methods can be envisaged to characterize the residual film left on the skin, such as biophysical methods like Corneometer®, Sebumeter®, Glossymeter® (Calixto et al., 2018; Lukic et al., 2012); infrared spectroscopy (Prasch et al., 2000; Wichrowski et al., 1995); contact angle measurements (Eudier et al., 2019b), or the combination of all these techniques (Faucheux et al., 2020). All these studies proved that the organisation and interaction of the ingredients inside the matrix have an impact on the properties of the residual film and, as a consequence, on the interaction with the human skin. The Pickering emulsions, being different in terms of composition from the classical emulsion, are expected to form a residual film with original properties. For this reason, the authors investigated the interactions between the emulsions and the human skin surface once applied, focusing on the

residual film properties, and thus bringing novel information in the field of the applicative properties of the topical Pickering emulsions.

In this article, nine emulsions were studied, stabilised by different metal oxides, usual surfactants or a mixture of both. The work focuses on metal oxide particles like TiO_2 and ZnO, poorly studied till now in the skin application field, contrary to the silica particles. According to (Peito et al., 2022), the only work on the Pickering topical application stabilised by titanium dioxide was performed by (Marto et al., 2016a, 2016b). The results of their work were potentially interesting; however, the formulation was highly charged in metal oxides, containing 35% of solid particles (TiO_2 and ZnO), contrary to this work, not exceeding 10% of metal oxides, being more suitable for the pharmaceutical topical use.

The first aspect that was considered was the homogeneity of the residual film when the cream was applied to the skin. Depending on the particles selected and emulsion composition, the physicochemical properties of formulations, i.e. microstructure and viscoelastic properties, were studied and related to the spreading behaviour of Pickering emulsions. Finally, the last step consisted of the investigation of human skin's role in the formation of the residual film. The skin is a biological system, extremely complex and with particular physicochemical properties. Therefore, to describe the skin–Pickering emulsion interactions in terms of spreadability, friction behaviour and residual film after application - a combined approach with *in-vivo* and *in-vitro* analyses at the skin and skin substitute surface was used.

2 Materials and methods

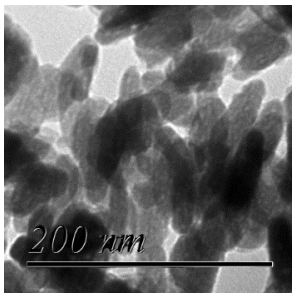
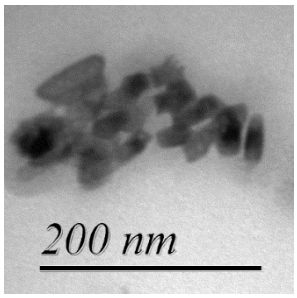
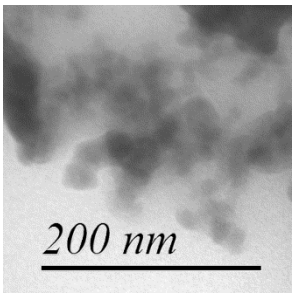
2.1 Materials

The ingredients (of dermo-cosmetic grade) used in this work were offered by the suppliers. The use of the dermo-cosmetic grade particles allows further application of the products on the skin, with no risk of toxicity issues, contrary to the modified particles often used in literature, which should be evaluated to ensure human safety (Peito et al., 2022).

Three types of particles were used, kindly offered by the suppliers of the raw materials:

Table 1. Trade name and the supplier of raw materials, INCI (International Nomenclature of Cosmetic Ingredients), CAS and the particle size, as well as the average particle size, measured by Transmission Electron Microscopy

Trade name (supplier)	**Eusolex® T-Easy (Merck)**	**ZnO-750-NJE7 (Kobo)**	**Aerosil®200 (Evonik)**
INCI	Titanium Dioxide, Silica, Cetyl phosphate	Zinc Oxide, Jojoba Esters	Silica Cetyl silylate
CAS	13463-67-7; 7631-86-9; 3539-43-3	1314-13-2; 61789-91-1	199876-45-4
TEM			
Measured particle size (nm)	L 76 ± 16 l 23 ± 3	L 51 ± 12 l 19 ± 4	L = l = 28 ± 4

The particle size of the studied particles was evaluated by transmission electron microscopy (Table 1). Observations were made with a FEI Tecnai 12 Biotwin transmission electron microscope operating at 80 kV, with ES500W Erlangshen CCD camera (Gatan).

To complete or replace the solid particles in the emulsions, a classical emulsifier was used, composed of two ethoxylated ethers: Steareth-2 (Massocare® S2) is a polyoxyethylene (2) stearyl ether and the Steareth-21 (Massocare® S21) is a polyoxyethylene (21) stearyl ether (Ash, 2004), all supplied by Massó. The mixture is used for topical applications and is well known for its stabilizing properties (Pasquali et al., 2008). The choice of this excipient was inspired by the previous studies of nanoparticle-based emulsions (Rossano et al., 2014; Rowenczyk et al., 2016).

Finally, the oil phase chosen for the project was Caprylic capric triglycerides (CCT), with the trade name Triglycerides C8C10 55/45 was offered by Stéarinerie Dubois (CAS 73398-61-5), while the preservative, coming from Seppic, was a blend of Phenoxyethanol and Methylparaben and Ethylparaben and Propylparaben and Butylparaben, under the trade name Sepicide HB (122-99-6; 99-76-3; 120-47-8; 94-13-3; 94-26-8).

2.2 Emulsions

To formulate stable and totally emulsified systems, the chosen particles and emulsifier were used at different concentrations (Table II):

Table II. Emulsion code and the associated type and quantity of stabilizing systems, varying between 4% and 10%.

Emulsifying system	TiO_2 10	TiO_2 4	ZnO 10	SiO_2 4	TiO_2 5St 5	ZnO 5St 5	SiO_2 2St 2	St 10	St 4
TiO_2	10%	4%	-	-	5%	-	-	-	-
ZnO	-	-	10%	-	-	5%	-	-	-
SiO_2	-	-	-	4%	-	-	2%	-	-
Steareth-2/Steareth-21 (60/40)	-	-	-	-	5%	5%	2%	10%	4%
Total quantity of emulsifying system	**10%**	**4%**	**10%**	**4%**	**10%**	**10%**	**4%**	**10%**	**4%**

The idea was to use the optimal concentrations of metal oxides for the emulsion stabilisation, depending on the type of the solid particles (4% and 10% for TiO_2, 10% for ZnO and 4% for SiO_2). Then, several emulsions were

formulated as a 50/50 mixture of both stabilising systems to investigate the role and dominancy of each stabilizer.

To complete the emulsion, Caprylic capric triglycerides were used as the oil phase and its concentration in each emulsion was calculated to correspond to a 40% oil and 60% water ratio. The preservative was introduced at a 1% concentration to avert bacterial proliferation.

Objectives: The formulated emulsions were required to exhibit stability both at the microscopic and macroscopic levels. Their long-term stability was confirmed without surfactants. Additionally, systems containing both particles and surfactants were studied to investigate the potential synergy or exclusivity of one emulsification system over another.

During the formulation process, the particles were first pre-dispersed in the water phase for TiO_2 and SiO_2, and in the oil phase for ZnO. Next, the internal phase is added to the continuous phase under stirring to form an emulsion. For the Steareth stabilized emulsions, the oil phase, containing the emulsifier, was heated up to 80°C to melt the surfactant, before the emulsion formation. The addition of the preservative prevented the contamination of the emulsions for the next possible skin application.

The detailed composition and the formulation procedure, the stability monitoring, as well as some physicochemical properties were described in previous work (Terescenco et al., 2020).

2.3 Methods

2.3.1 Physicochemical characterisation

2.3.1.1 Microscopy under bright light

The structural organization of the samples was studied by employing the digital camera of a Leica DMLP microscope (DMLP/DC 300, Leica Microsystems, Wetzlar, Germany). The micrographs, presented in the study, were taken at a magnification of x100, transmission mode and recorded with Leica Application Suite Software.

2.3.1.2 Rheological measurement

The analyses were performed with a controlled stress rheometer (HR2, TA instruments). The oscillatory tests were realised at 25°C. In order to preserve the form of the droplets under the 60 mm aluminium parallel-plate geometry, a gap corresponding to the minimum triple size of the studied droplets was fixed at 200µm. Before each analysis, an interval of 120 seconds is respected once the geometry is in the position, necessary for the sample restructuring.

The conditions of the oscillatory test: frequency = 1Hz, strain variation = 0.1% - 100%. Collected parameters: in the linear viscoelastic region: G' (elastic modulus), tan δ (=G"/G'), as well as $\gamma_{90\%G'}$ and $\gamma_{G'=G''}$. $\gamma_{90\%G'}$ is the endpoint of the linear viscoelastic region, it is fixed at the strain (%) when the storage modulus (G') value loses 10% from the linear level (Korhonen et al., 2002). $\gamma_{G'=G''}$ is the strain value when elastic modulus equals the viscous one (G'=G") which coincides with a loss of viscoelastic properties and the transition to the product flow process.

2.3.1.3 Texture analysis – spreading test: In-vitro spreadability test

To perform the spreading test, the TAXT Plus apparatus (Stable Micro Systems, Cardiff, UK) was used, equipped with friction module A/FR (ASTM-D 1894-90). To imitate the surface of the skin, a polypropylene plastic sheet was used, fixed to the base of the texturometer. 200µL of the emulsion is spread by the sled over a 120mm distance at a constant speed of 3mm/sec. The force necessary to spread the emulsion is registered. The test conditions were adapted from similar studies of the spreading properties developed by Gilbert *et al.* (Gilbert et al., 2013b) and (Savary et al., 2013).

2.3.2 *In vivo* analysis - Skin product interaction at the surface: *in-vivo* and *in-vitro* analyses

Studies further described involved human subjects and were carried out following The Code of Ethics of the World Medical Association (Declaration of Helsinki) and have been approved in advance by the local institutional ethics committee at UNILEHAVRE (France). All subjects participated only after receiving detailed oral and written information and signing an informed consent agreement.

A microbiological test was performed (ACM, Bellegarde, France) to confirm that each product was in accordance with the dermo-cosmetic criteria for bacterial contamination (< 100 UFC/g or/ml) for both the search for aerophilic mesophilic bacteria (AFNOR, 2017a) and the enumeration of yeasts and moulds (AFNOR, 2017b). Because all the samples presented <10 UFC/ml, they were judged as suitable for the sensory analysis.

The study was performed on two surfaces: human skin and one non-biological surface. The non-biological surface was used in order to bring complementary information to the tests performed *in vivo* through a different analytical approach. The non-biological surface chosen for the study was the BioSkin.

The artificial BioSkin Plate #30 was supplied by Beaulax, Co. Ltd, Tokyo, Japan. BioSkin is composed of two layers of polyurethane elastomer (Giron et al., 2016) mimicking skin elastic and viscoelastic properties (Jachowicz et al., 2007). This surface was chosen for the study because it has been already used to characterize powder foundation properties (Ikeda et al., 2014), the properties of thin films applied on the skin (Sato et al., 2016) and the prediction of the residual film perception of cosmetic products (Eudier et al., 2019a).

2.3.2.1 Contact angle measurements

First, the contact angle measurements were performed on the pellets of the three analysed particles: TiO_2, ZnO and SiO_2. For this purpose, 20 mg of each particle were compressed under 5 tonnes to form compact pellets.

Then, the contact angle measurements were performed on the human skin (panel composed of nine women aged between twenty-one and forty years) and on the artificial skin models. 40µL of the product was placed in the middle of the circle (Ø 5cm) drawn on the inner surface of the forearm or the skin model. The product was spread using the forefinger by covering the entire surface within the circle, till 50 circles with the speed of 90 RPM. The contact angle was measured one minute after the emulsion application.

A portative goniometer PGX+ (ScanGaule, Gravigny, France) was used. The photos of liquid droplets deposited onto the surface were taken with a high-resolution camera associated with a mirror. The advanced contact angle is calculated using a succession of five drops. The volume of the final drop was approximately 7µL. Photography was taken after each liquid addition. The software PGPlus calculated the contact angle of each drop. The retained value is the maximum obtained from all five drops. At least three repetitions were performed for each measure. The protocol was adapted from (Eudier et al., 2020).

2.3.2.2 Biometrological analysis

The clinical study was conducted in the Biometrology analysis room at the University of Le Havre Normandy (Le Havre, France) with controlled temperature (20–22°C) and humidity (45–55%). Sixteen women aged from 20 to 50 years were included in the study. Subjects performed acclimatization for 10 min before measurement. The formulations were applied to five regions of a 4×5 cm area located on the forearm. The measurements were performed first with no product applied and one minute after the application of 40 µL of the formulation. The measurements were performed by the same operator in triplicate.

2.3.2.2.1 Friction measurement

A Frictiometer® FR700 equipped with a plain, smooth Teflon (PTFE) disk (16mm of diameter) (Courage-Khazaka electronic GmbH MPA580, Germany) was used to measure the skin friction coefficient. The measurements were made at 90 RPM (as for the application of the formulation) during 120 s. The computer software readily returned the data in arbitrary units (A.U), to express the force necessary to move the Teflon disk on the surface to assure the correct speed of rotation.

2.3.2.2.2 Film glossiness

The specular reflecting light from the skin was evaluated with a GL 200 Glossymeter® (Courage-Khazaka, Germany). The device evaluates the brightness of the skin surface by measuring the reflected light (Calixto et al., 2018; Try et al., 2010). The measurements were performed at least in triplicate for each studied zone, chosen by the operator.

2.3.2.2.3 Film colour

The skin colour was measured before and after the application of the product with CL 400 Colorimeter®. The probe sends out white LED light, arranged circularly to uniformly illuminate the skin. The emitted light is scattered in all directions, some parts travel through the layers and some are scattered out of the skin, the light reflected from the skin is measured in the probe and expressed accordingly. Measuring values are expressed as coordinates in the colour space L*a*b*. The results of this study were described by two values:

- L* gives information about the black-white-axis
- The b*-value located on the yellow-blue axis

2.3.3 Data analysis

In the article, numerical data are given as mean value ± standard deviation (SD).

To statistically analyse the collected results XLSTAT software (Version 2016.02.27444, Addinsoft, Paris, France) was used. The way analyses of variance ANOVA test were applied to the results. The significant differences between the emulsions ($P<0.05$) were then identified depending on each studied parameter. A multiple comparison test was further used to distinguish different groups of products (Tuckey).

3 Results and discussion

3.1 Macrostructure and microstructure of the studied systems

The use of emulsions as a pharmaceutical vehicle demands perfect control of its properties.

Some of the physical properties of these emulsions were determined previously (Terescenco et al., 2020) and made possible to give the following information :

- *All the systems are capable of stabilizing the oil/droplet interface and thus obtaining droplets of different sizes (Table 3).*
- *For the systems containing exclusively the metal oxides, the droplet formation indicates the particles' ability to stabilize the interface and confirms the formation of Pickering systems.*
- *It has also been demonstrated that when a surfactant/particle combination is used, it is the surfactant that plays the main role in emulsion formation and replaces the particle at the water/oil interface.*

Table 3. Emulsions type (water in oil for W/O or oil in water for O/W) and the D[4,3], the volume mean diameter, obtained by static light scattering (SLS) measurements, from (Terescenco et al., 2020)

Emulsion	ZnO10 (W/O)	ZnO5St5 (W/O)	$TiO_2$10 (O/W)	$TiO_2$4 (O/W)	$TiO_2$5St5 (O/W)	$SiO_2$4 (O/W)	$SiO_2$2St2 (O/W)	St4 (O/W)	St10 (O/W)
D [4,3] µm	1,11±0,02	29,78±3,06	12,92±0,33	27,07±1,44	3,28±0,38	9,53±0,76	5,68±0,18	2,01±0,03	1,74±0,03

The complementary step of the study was to investigate the rheological behaviour of each formulation through a strain sweep test. The viscoelastic behaviour of the emulsions is resumed in Table IV. These experiments enabled obtaining the linear viscoelastic region (LVR), corresponding to G' and G" moduli independent from the applied strain amplitude. All the emulsions exhibited a predominant elastic behaviour ($\tan\delta<1$) within the LVR (Table IV). Also, tan δ values showed that the elastic properties were more dominant than the viscous ones for

the $SiO_2$4 emulsion (Korhonen et al., 2002) which can be due to the system's gelation by silica particles (Torres et al., 2007), making this system different from other Pickering systems. When the system is gelled, the stability during the long storage is excellent (Chevalier and Bolzinger, 2013). For the same amount (4 or 10%), the elastic modulus, G' within the LVR, related to the consistency of the system at rest was higher for the Pickering emulsions ($TiO_2$10, ZnO10, $TiO_2$4, $SiO_2$4) than the systems stabilized partially or totally by a classical emulsifier.

The endpoint of the LVR was determined as the point where the storage modulus G' plateau value dropped by 10% $\gamma_{90\%G'}$ (Gilbert et al., 2013a; Korhonen et al., 2002). Wide linear viscoelastic regions are a sign of the ability of structures to resist external stresses to a greater extent. The Steareth containing systems, as well as $SiO_2$4, showed better resistance to the deformation, with a wide viscoelastic region, pointing to the fact that Pickering emulsions are often more consistent, but at the same time more fragile.

$\gamma_{G'=G''}$ may be identified with the critical strain above which the structure starts to ''break down.'' It can also be shown that above another critical strain, G" becomes higher than G'. This is sometimes referred to as the ''melting strain'', at which the system becomes more viscous than elastic (Tadros, 2010). Impressively, the most important "melting strain" was observed for the ZnO-containing emulsions. The explanation of this phenomenon is certainly linked to the inverse organization of the emulsion, being of water in oil type.

Table IV. Calculated G' (Pa) and Tan δ values at the plateau; the plateau length expressed by oscillation strain point at 10% of G' plateau decrease; and the network destruction point represented by the oscillation strain value at G' and G" intersection, as well as the standard deviation values.

	$TiO_2$10	$TiO_2$4	ZnO10	$SiO_2$4	$TiO_2$5St5	ZnO5St5	$SiO_2$2St2	St10	St4
G' (Pa)	6535 ± 450	518 ± 15	2684 ± 208	5671 ± 283	126 ± 3	1065 ± 34	154 ± 4	370 ± 15	23 ± 0,2
Tan δ	0,175 ± 0,008	0,061 ± 0,002	0,178 ± 0,015	0,010 ± 0,001	0,351 ± 0,004	0,130 ± 0,006	0,383 ± 0,002	0,362 ± 0,003	0,535 ± 0,003
$\gamma_{90\%G'}$ (%)	0,28 ± 0,02	0,57 ± 0,01	0,13 ± 0,01	4,46 ± 0,14	3,00 ± 0,23	0,24 ± 0,01	1,87 ± 0,05	3,11 ± 0,32	4,85 ± 0,58
$\gamma_{G'=G''}$ (%)	8,8 ± 1,2	55,1 ± 6,7	73,4 ± 0,1	14,4 ± 0,4	49,9 ± 4,0	69,5 ± 2,0	12,0 ± 2,7	9,9 ± 1,2	46,4 ± 3,5

The quantity of the solid particles used for the system formulation is higher than the precise quantity necessary to stabilize the oil-water interface, thus there are excess particles present in the water phase (for the oil in water emulsions) and the oil phase (for the specific case of ZnO inverse emulsion). According to (Chevalier and Bolzinger, 2013), the excess particles often cause thickening of the emulsion and the same phenomenon was observed in our study. Indeed, a quantity of the particles serves to stabilize the interface, while the excess particles play a role in the macroscopic stabilization of the emulsion. They contribute to the formation of a three-dimensional network within the continuous phase, which is paramount for ensuring emulsion stability.

The study showed that 4% of TiO_2 particles can stabilize the oil-water interface, which means that in the case of 10% TiO_2 use, an important quantity of particles do not participate in the interface stabilization and will be dispersed in the continuous phase. The G' modulus of TiO_2 10% was ten times higher than the TiO_2 4% system at rest but at the same time, the system is more fragile and resists less to the oscillation.

The obtained results showed that the rheological behaviour of the formulations was impacted by the excipients used to stabilise systems and also by the particle type when used. Pickering emulsions were more consistent but with a lesser resistance to the deformation. To complete this characterisation, the behaviour of emulsions was studied during application using a mechanical spreading test. The textural spreading test was realized by spreading a precise quantity of the cream between two surfaces: Polypropylene and Polymethyl methacrylate (PMMA). The human skin has a surface energy of around 38.7 mN/m (Agache, 2004), while the surface energy of the polypropylene and PMMA is equal to 30.1 mN/m and 41.1 mN/m (Gooch, 2011), which can be considered as similar to the skin. This analysis is a predictive test to explore the spreading of topical creams on the skin (Gilbert et al., 2013b).

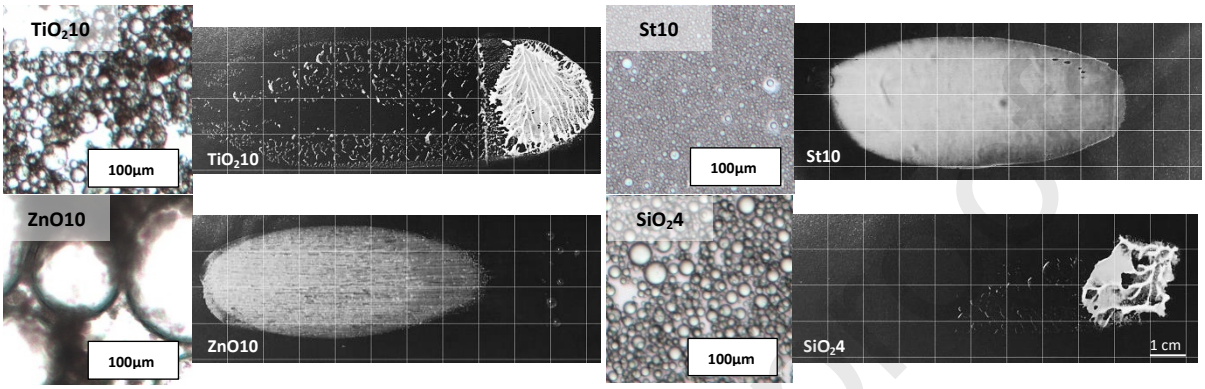


Figure 1. Microscopic organization (*100 magnification) of ZnO10, $TiO_2$10, St10 and $SiO_2$4 emulsions; the example of their spreading traces (spreading over 120 mm distance at 3 mm/sec between polypropylene and PMMA surface). The emulsions were spread from left to right.

The most remarkable spreading behaviours are presented in Figure 1 for ZnO10, $TiO_2$10, $SiO_2$4 and St10 emulsions. Emulsions exhibited extremely different spreading traces. This is related to the stabilising system (metal oxides or the classical excipient) and the emulsion orientation (ZnO10 – water in oil, $TiO_2$10, $SiO_2$4 and St10 – oil in water) as well as to the microstructure of the systems. In particular, the homogeneity of the spreading trace is dependent on both parameters: the emulsion microstructure and its affinity with the surface.

The emulsion microstructure plays a critical role in this parameter as revealed by the combination of the results of the droplet volume mean diameter (Table 3) and the most representative microscopic images. The TiO_2 and ZnO stabilized emulsions are the most fragile; however, their spreading behaviour differs significantly. Microscopic analysis of the $TiO_2$10 emulsion in Figure 1 reveals the polydispersity of droplet sizes and particle agglomerations in the continuous phase, indicating that the network will break down easily, as observed in the rheological test ($\gamma_{G'=G''}$ in Table IV). The spreading trace depicts a non-homogenous film with a low affinity for nonpolar surfaces, such as skin. Consequently, even though the system is quickly destroyed, the sled will still pull the remainder of the emulsion to the end of the studied distance.

The ZnO10 emulsion demonstrates the shortest trace and minimal product distribution, indicating its inherent difficulty in spreading due to the inverse water-in-oil phase organization. While microscopic examination reveals visually discernible large droplets (>100µm) within the system, yet the calculated mean diameter of droplets obtained from static light scattering (SLS) results is substantially smaller (1,11±0,02 µm). This discrepancy suggests that the droplets observed under microscopy undergo disruption during sample preparation for SLS analysis. For the spreading test, the previous observation underscores the susceptibility of the microstructure to break down, even from the mere placement of the sled on the emulsion. Due to its affinity with the polypropylene sheet, a predominant concentration of the product is observed at the beginning of the experimental distance.

Moreover, it is interesting to notice the “quick breaking” effect, with the water liberation at the end of the spreading. It is a specific behaviour of a water-in-oil emulsion which, upon application to the skin, breaks open and releases visible drops of water (quick-breaking emulsions) (Ratschow et al., 2015), as could be seen in Figure 1 (the end of the ZnO10 trace).

The St10 containing emulsion presents a homogenous spreading trace, pointing to the resistance of the system, but also the strong droplet interactions (as shown on the micrograph in Figure 1) as well as the affinity with the

surface. All the emulsions containing the Steareth emulsifier presented a similar visual spreading trace. The $SiO_2$4 emulsion presents an organized microstructure, with spherical droplets and a network organization, as can be seen from the micrograph, with the mean diameter of droplets approaching a conventional emulsion (9,53±0,76 µm); however, its spreading profile is not similar to the Steareth stabilized emulsion, pointing at the lower affinity with the surface. These examples show the strong dependence between the type of stabilizing system and the final spreading trace. For the emulsions containing particles and surfactants, the spreading trace is more homogenous (data not shown) similar to the St10 emulsion.

To resume, when linking both tests, rheological and textural, one should consider the flexibility of the system during the solicitation, which can be assimilated with LVR plateau length: the systems containing the Steareth-2/21 excipient have higher $\gamma_{90\%G'}$ values, pointing at the better resistance to the deformation. The particle-containing emulsions, without a strong connection between the droplets, lose quicker their homogeneity during the application. Meanwhile, the SiO_2-containing systems behave differently from other ones. The $SiO_2$4 emulsion shows a long plateau length due to the gelation capacities of the silica particles, resulting in the formation of a strong 3D droplet network but with a non-homogeneous spreading film. Consequently, the viscoelastic properties are not sufficient to describe the spreading behaviour of the Pickering emulsions; one also should consider the interaction between the system and the surface using, for example, contact angle measurements.

3.2 Contact angle and biometrologic results

The next step aims to investigate the impact of the solid particles on the skin surface after application. According to the literature, the increased activity and efficacy of Pickering emulsions in topical biomedicine are linked directly to the design of the particulate emulsifier agents. These particles often demonstrate enhanced adhesion, resulting in increased skin adhesion and hence improved delivery efficacy (Harman et al., 2019; Laredj-Bourezg et al., 2017).

First, the contact angle measurements were performed on the compressed pellets. The studied particles revealed different behaviours, as can be seen in Figure 2. TiO_2 particles coated with silica and cetyl phosphate showed a hydrophobic behaviour, which is even more pronounced for the ZnO particles coated with jojoba esters. Unexpectedly, the SiO_2 cetyl silylate exhibited a contact angle of 17,1°. According to (Wu et al., 2020) the contact angle measurement by a drop of water on a glass substrate coated with fumed silica particles of the same type equals 50°. However, while measuring the contact angle on the pellet, the mechanism was more governed by the penetration and not by the spreading of the liquid on the pellet. This result reveals the high porosity of the compressed pellet (specific surface of the particle 170-210 m^2/g according to the supplier) and not its coating/water interaction.

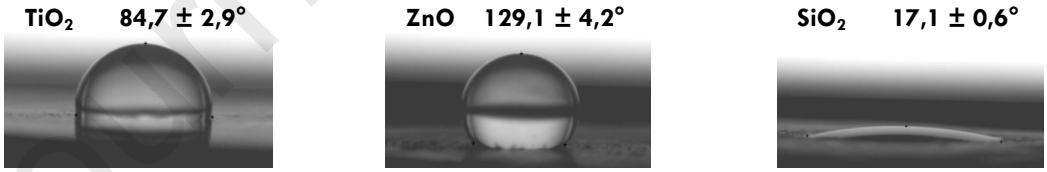


Figure 2. Images of the droplets and calculated values of the contact angle formed by a water droplet on TiO_2, ZnO or SiO_2 pellets respectively.

During the next step, the residual film of each formulation was analysed. First, the contact angle measurements were performed on the human skin. Nine emulsions were then applied to the surface to form a thin film of the product. Figure 3 demonstrates the shape of the water droplet deposited on the residual film present on the skin. The statistical data are resumed in Table V.

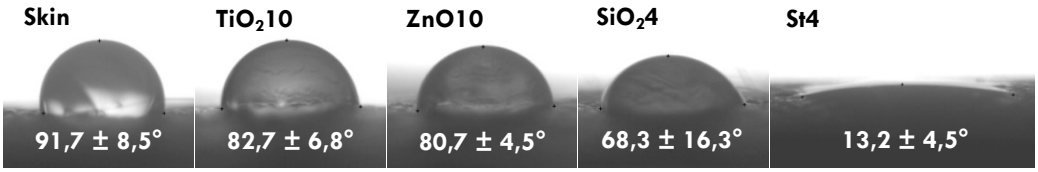


Figure 3. Images of the droplets and calculated values of the contact angle formed by a water droplet on the skin and the emulsion films (containing 10% of TiO_2, 10% of ZnO, 4% of SiO_2 or 4% of Steareth-2/21) applied to the skin.

One can observe, from Figure 3, that the emulsions stabilised solely by the particles possess a level of hydrophobicity close to the human skin with values ranging from 68.3 to 82.7°. Consequently, these systems can be tested as surfactant-free mineral sunscreens with a high potential for water resistance (Marto et al., 2016b). (Hagens et al., 2007) proved that contact angle measurement can predict the water resistance of the sunscreens. The authors claim that formulations that give contact angle values above 30° may be categorized as water-proof without further testing by SPF/immersion/SPF technique, this being the case of our TiO_2, ZnO and SiO_2 formulations.

Meanwhile, all the emulsions containing Steareth-2/21 emulsifiers are highly hydrophilic independently of the presence or the type of solid particles (Table V) with values ranging from 13.2 to 20.8°.

Table V. The average contact angle, friction (Frictiometer®) and gloss (Glossymeter®), as well as L* and b* (Colorimeter®) values collected on the human skin before and after application of the nine studied emulsions. Complementary, the b* value on the artificial skin model (Bioskin®) is given. A-F Values in a line with a different letter indicate that corresponding products are significantly different (P<0,05)

	Skin	BioSkin	$TiO_2$10	$TiO_2$4	ZnO10	$SiO_2$4	$TiO_2$5St5	ZnO5St5	$SiO_2$2St2	St10	St4
Contact angle (°)	91,7		82,7	78,5	80,7	68,3	15,4	20,8	19,9	18,1	13,2
	A		**B**	**B**	**B**	**C**	**D**	**D**	**D**	**D**	**D**
Friction (A.U.)	377,0		574,8	600,6	435,7	527,1	507,0	423,2	434,9	316,6	283,2
	F		**B**	**A**	**E**	**C**	**D**	**E**	**E**	**G**	**H**
Glossiness (A.U.)	3,8		5,1	5,2	6,1	5,3	5,6	5,7	5,7	6,7	6,2
	D		**C**	**C**	**AB**	**C**	**BC**	**BC**	**BC**	**A**	**AB**
L* (Human skin)	68,5		71,3	69,9	70,7	69,5	69,9	69,9	69,7	70,3	70,1
	B		**A**	**AB**	**A**	**AB**	**AB**	**AB**	**AB**	**A**	**AB**
b* (Human skin)	9,6		6,4	8,3	8,4	9,4	8,9	8,8	9,0	9,2	9,3
	A		**C**	**B**	**AB**	**AB**	**AB**	**AB**	**AB**	**AB**	**AB**
b*		17,7	7,4	8,9	13,8	17,0	11,1	14,1	17,1	16,6	17,3

(BioSkin)	**A**	**F**	**E**	**C**	**AB**	**D**	**C**	**AB**	**B**	**AB**

There are few studies focused on the tactile properties of the Pickering emulsions used as topical vehicle systems. Some recent interesting investigations were performed by (A. Ali et al., 2022) on the tactile friction of Pickering emulsions stabilized by modified quinoa starch on the excised porcine skin and Vitro-Skin. In our study focusing on the properties of the specific residual film formed by Pickering emulsions on the human skin, the Frictiometer® was used. Several studies on nano-TiO_2 and/or nano-ZnO particles (Filipe et al., 2009; Schilling et al., 2010) reported no evidence of healthy skin penetration beyond the stratum corneum. Only in the case of skin lesions scheduled for plastic surgery, some particles can penetrate the deeper substrates (Tan et al., 1996). It means that all the particles will be retained at the surface of the skin and will affect the properties of the film.

Table V shows the impact of the particle type and quantity on the friction values, obtained on the human skin.

First, it should be observed that all the particle-containing emulsions have higher friction than the bare skin (friction of 377 A.U.), while the Steareth-2/21 at 4% and 10% reduce the friction values acting as a lubricant. The presence of the TiO_2 particles in the $TiO_2$4 and $TiO_2$10 emulsions leads to the most important friction values, with 600.6 and 574.8 A.U., respectively. The rotation of the Teflon disk is also more difficult for the $SiO_2$4 emulsion. (Timm et al., 2012) demonstrated that a correlation was found between the friction coefficients determined in vitro and the perceived skin feel after the application of an aqueous suspension containing powder particles on the human skin. It is interesting to notice that the sensory perception of the "screech residue" performed during the sensory analysis (Terescenco et al., 2020) is identical to the results of the friction test. It means that the "roughness" of the film can be easily perceived by a patient during application also for the more complex systems of emulsion type. This tactile property is not always well accepted and could therefore be a condition of rejection for the use of a topical product for a local delivery of a drug. Moreover, the properties of the film change as a function of the emulsion composition: $TiO_2$5St5 emulsion, containing 5% of the TiO_2 particles gives smaller friction values than the $TiO_2$4 emulsion containing 4% of metal oxides, due to the presence of the Steareth-2/21, which plays a role of a lubricant. Also, the emulsion orientation, water in oil, makes the film of the ZnO10 emulsion more slippery, even containing 10% of metal oxides.

Additionally, the results for the glossiness of the film are given in Table V. The no-particle-containing products (St10 and St4) gave the glossiest films, followed by the inverse W/O ZnO10 emulsion. An equal mix of particles and conventional emulsifiers reduces the film glossiness, while the systems O/W containing only metal oxides ($SiO_2$4, $TiO_2$4 and $TiO_2$10) blur the glossy effect of the oil phase with the lowest values. In all cases, the glossiness value is higher than the skin without any product due to the presence of the oil phase.

To evaluate the effect of the solid particles on the colour of the residual film, Colorimeter® analyses were carried out. The results were collected in L*a*b representation. The L* parameter for the CIELAB colour space expresses the lightness from black (0) to white (100). It was expected that the white particles of TiO_2, due to their covering properties, would importantly change the skin colour. But, as can be seen from Table V, the results on the human skin are quite identical, no statistical discrimination was observed. Knowing that the human panel could visually differentiate the emulsions (Terescenco et al., 2020), a complementary approach was carried out. The b* parameter for the CIELAB colour space expresses the variation from blue (−) to yellow (+) and it was further analysed. The bluish effect of the TiO_2 particles allowed their discrimination from the other emulsions, but all the other systems remained statistically identical. Still, the obtained results were less discriminant than a human panel. Another approach was then used. Namely, a synthetic skin model, Bioskin, was used to replace the human skin for a similar test. The b* parameter in the Bioskin (Table V) formed three groups: TiO_2 – the most important "bluish" effect; ZnO – the "bluish" effect of the particles still observed; other products – no important whitening effect. The Colorimeter® analysis was expected to give more efficient results than the sensory analysis by a human panel, but it was shown that for the residual film colour perception, the human eyes remained a confident and representative instrument together with the use of a synthetic skin model associated with Colorimeter® analysis.

4 Conclusion

By concentrating on Pickering emulsions, the novelty of this study lies in investigating the diverse properties of residual films following application to the skin. To comprehend the influence of these systems, three distinct types of solid particles were chosen to formulate macroscopically stable emulsions: Titanium dioxide (coated with Silica and Cetyl Phosphate), Zinc oxide (coated with Jojoba esters), and Silica Cetyl Silylate. These same particles were employed to formulate emulsions with mixed particle/emulsifier combinations. Finally, two emulsifier-stabilised creams served as references in this study.

When examining the properties of the residual film in the studied systems, two categories were observed: Pickering emulsions and emulsions containing partially or exclusively classical emulsifiers. In the latter scenario, it is the Steareth-2/21 emulsifiers that govern microstructure organization, thereby influencing the physical response of the products to external stimuli. Moreover, upon application to the skin and disruption of the system, they generate a highly hydrophilic film. This chemical response of the steareth-2/21 molecules remained unaffected by the presence or type of solid particles in the formulation.

In the case of Pickering emulsions, each particle individually influenced its properties. TiO_2 and SiO_2 formed oil in water emulsions, while ZnO particles oriented the emulsion towards the water-in-oil type.

TiO_2 Pickering emulsions were consistent, but also easily breakable systems. They formed a non-homogeneous spreading trace during the application, with a hydrophobic residual film. Finally, this well-known UV filter, which does not penetrate the skin and stays on the surface, impacted the friction parameter, provoking the “roughness” of the residual film, its whitening effect and the blur of the oil phase glossy effect.

The ZnO Pickering emulsion, due to its inverse orientation, showed original viscoelastic behaviour, less consistent than TiO_2 and the most fragile compared to the other systems. Its distinctive microstructure created the “quick breaking” effect observed during the application of the emulsion. However, the affinity between the external oil phase and the nonpolar surface used for the spreading test made it possible to obtain a more homogeneous trace than TiO_2. Finally, the water-in-oil organisation of this system reduced the roughness of the residual film, its whiteness and glossiness, while still being highly hydrophobic.

The SiO_2 system showed a unique behaviour compared to the other systems. The gelation of the silica particles made this emulsion one of the most consistent, solid and resistant than other metal oxides, even at a low concentration. The strong silica gel emulsion is difficult to spread, forming a non-homogeneous trace. The residual film is hydrophobic, still rough and with reduced gloss. However, this type of stabilising particle does not affect the colour of the film after application to the skin.

As mentioned earlier, within systems containing the emulsifier/particle mixture, the stabilization process is primarily regulated by the emulsifier. The emulsion structure of the hybrid systems closely resembles that of the reference emulsions. However, certain distinctive properties, such as roughness and coloration of the residual film, are directly attributable to the presence of particles within the system.

Declaration of Interest

None

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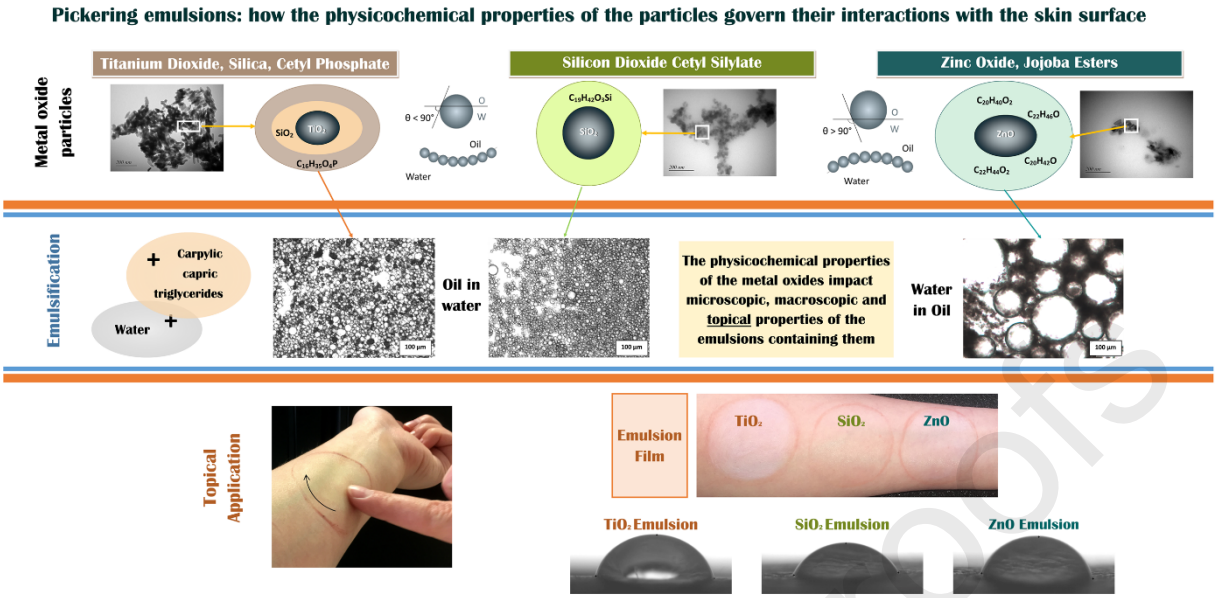

5 Declaration of Interest

None