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Original Article

In Vitro Testing of Sunscreens for Dermal Absorption: A Platform for Product Selection for Maximal Usage Clinical Trials

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Abstract

Sunscreen products contain UV-filters as active ingredients for the protection of skin against UV radiation. FDA issued a new proposed rule in 2019 (84.FR.6204) for sunscreens and identified the need for additional safety data for certain UV-filters including their dermal absorption data. Dermal absorption data reveals systemic exposure of UV-filters in humans, which can be obtained from clinical maximal usage trials. FDA guidance recommends conducting *in vitro* skin permeation tests (IVPT) to help select formulations for maximal usage clinical trials, as IVPT results may be indicative of *in vivo* absorption. This case study reports *in vitro* methodologies used for the selection of sunscreen products for an FDA-sponsored proof-of-concept maximal usage clinical trial. An IVPT method was developed using human cadaver skin. Commercially available sunscreen products were tested to determine the skin absorption potential of common UV-filters using this IVPT. All the studied sunscreen products demonstrated a certain degree of skin absorption of UV-filters using IVPT, and a formulation rank order was obtained. These sunscreen products were also characterized for several formulation properties including the globule size in emulsions, which was found to be an indicator for the rank order.

Key words: Sunscreen, UV-filters, Skin, Absorption, Maximal usage

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1. Introduction

UV-filters are active ingredients in sunscreen products. They function to protect the skin from sunburns and UV-related skin damage. These small molecules protect the skin by absorbing, scattering, or reflecting UV radiation. Ideally, UV-filters are intended to work on the skin surface without penetrating the skin and thereby reaching the systemic circulation. However, UV-filters such as oxybenzone have been detected in the systemic circulation (Calafat et al., 2008, Janjua et al., 2008, Matta et al., 2019). Sunscreen products are recommended for frequent, daily application in quantities that may result in coverage of up to 80% of the body surface (Heerfordt et al., 2018). Therefore, application of sunscreen ingredients may lead to systemic exposure in a single day (Hayden et al., 1997, Janjua et al., 2004, Matta et al., 2020, Matta et al., 2019, Michele, 2018) and substantial exposure over a life-time.

Sunscreen products are regulated as cosmetics in some countries. However, in the United States, sunscreens are regulated as drug products, primarily under the over-the-counter (OTC) drug monograph system (FDA, 2019a). Despite increasing use across a broad population, there are limited data on whether or to what extent UV-filters are systemically absorbed from various sunscreen formulations and whether there are adverse effects from systemic exposure (Adamson and Shinkai, 2020). Therefore, evaluating the extent of absorption of common UV-filters is important for public health. Different excipients in sunscreen formulations could enhance the absorption of UV-filters to different degrees. Therefore, it is important to evaluate the absorption of active ingredients from a representative range of formulations. In 2019, the FDA issued a new sunscreen proposed rule (monograph) (FDA, 2019c) on “sunscreen drug products for over-the-counter human use”. This rule requests additional data to determine if certain active ingredients

listed in the 1999 Final Monograph (FDA, 1999) are generally recognized as safe and effective (GRASE) in sunscreen products.

One of the approaches to determine systemic exposure is conducting clinical trials under maximal-usage conditions (MUsT) (FDA, 2019b). Per the 2019 published MUsT Guidance for Industry (FDA, 2019b), *in-vitro* skin permeation testing (IVPT) is recommended to guide the selection of formulations to include in the MUsT. Formulations selected for evaluation by MUsT should be those with the highest potential for absorption of UV-filters. In this case study, we aim to use *in vitro* approaches to guide the selection of products for a proof-of-concept MUsT study (Matta et al., 2019). Although general IVPT guidelines are available (FDA, 2016, OECD, 2004), studying *in vitro* skin absorption of UV-filters is challenging because of their diverse physiochemical properties and combined presence in sunscreen products (**Table S1**). Existing studies in the literature have weakness in study designs or insufficient data which limit utility (FDA, 2019c, Oh et al., 2019) as definitive methodology for testing UV-filters. Therefore, we created a pilot IVPT in order to explore parameters useful for the purposes of guiding formulation selection for further clinical absorption testing. In addition, formulation characteristics of sunscreen products such as emulsion types, distribution of UV-filter, and globule sizes were evaluated for their influence on skin absorption.

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2. Results and Discussion

There is complex interplay among the properties of the UV-filters, the sunscreen formulations, and the IVPT outcomes. Physicochemical properties of the chemicals such as molecular weight (MW), melting point (MP), partition coefficient (log*P*), and topological polar surface area (TPSA), etc. are known predictors for skin absorption potential. Skin absorption is expected if the chemical's log*P* is between -1 and 4, MW is less than 500 g/mol, MP is less than 200˚C, or TPSA is less than 120 $Å^2$ (SCCS, 2015). All UV-filters studied have at least one physicochemical property that meets these criteria for skin absorption (**Table S1)**. Avobenzone and octocrylene have log*P* values greater than 4, indicating their skin permeability could be lower than oxybenzone, ecamsule, and parabens, whose log*P* values are lower. The IVPT results confirmed these predictions.

In the present study, the skin absorption of UV-filters was found to be influenced by the formulation. For example, the results in **Figure 3** show that the extent of absorption of oxybenzone following topical administration of cream, lotion and spray is different. Various formulation characteristics, such as the presence or absence of permeation enhancers, emulsion type, drug distribution, and globule size (Frelichowska et al., 2009), may play a role in skin absorption. Globule size of emulsion formulations is thought to be relevant to drug release and skin absorption of active ingredients. Therefore, semi-solid sunscreen formulations were characterized for their globule sizes.

2.1 Determination of emulsion type and distribution of UV-filters in semi-solid sunscreen products

Globule size may be critical for drug release only if globules contain the active ingredients. In the present study, emulsion type and the distribution of UV-filters in sunscreen emulsions (cream and lotions) were determined using Raman microscopy to see if most of the UV-filters were present in the globules. Raman spectra were obtained for the USP reference standards of each analyte in the formulations (**Figure 1a**). Circular globules in the sunscreen matrix for all three products were observed from an optical montage (**Figure 1b**). The averaged spectra for each emulsion phase (matrix and globules) were overlaid and compared (**Figure 1c**). While it is expected to see peaks related to the UV-filters present in both phases, the cream showed a larger contribution for peaks matching octocrylene and avobenzone (e.g. 404, 1297, 1595, 1607 and 2218 cm^{-1}) in the globules while ecamsule (e.g. 1184 and 1638 cm^{-1}) had a larger relative contribution to the Raman spectra obtained from the surrounding matrix. Ecamsule is the least hydrophobic among all the UV-filters studied (log*P* 1.4, **Table S1**), being mostly in the matrix indicates that the cream is an oil-in-water emulsion. Both lotions showed a stronger signal for the hydrophobic APIs (octocrylene, avobenzone and oxybenzone) in the globules relative to the matrix (**Figure 1c**), indicating that the lotions are also oil-in-water emulsions. Distribution of the UV-filters in the cream was further confirmed using confocal Raman mapping and multivariate image analysis (**Figure 1d-f**). Since all emulsions studied are of the oil-in-water type, and the UV-filters are mostly present in the globules, following application to the skin these formulations are expected to exhibit similar release profiles for avobenzone, octocrylene, and oxybenzone.

2.2 Globule size determination using cryogenic scanning electron microscopy (Cryo-SEM)

The size of oil globules in emulsions may have an effect on drug release rate and skin permeation efficiency (Doucet et al., 1998). Therefore, globule size was characterized using Cryo-SEM. Two distinct magnifications (500× and 2500×) were selected for appropriate display

of the globules (**Figures 2a-c**). Both lotions contain globules within the size range of 1-5 μm in diameter. A-lotion also contains a small fraction of larger globules that varied in size (10-25 μm, **Figure 2b)**. Image analysis of the cream sample did not yield globules in the 1-5 μm size range but did reveal a broader distribution of globules between 5-25 μm in diameter. Histograms were created (**Figure 2d**) and each histogram was fitted with a log normal distribution which was later used to calculate the mean and standard deviation of globule diameters of each sunscreen product (**Figure 2d** inset). The mean globule size was found to be 2.4 ± 0.8 μm for B-lotion, 3.1 ± 1.7 μm for A-lotion, and 9.4 ± 3.7 μm for the cream. Literature reports that microspheres smaller than 3 μm distribute randomly in the stratum corneum. In contrast, microspheres larger than 10 μm do not penetrate but remain on the skin surface (Frelichowska et al., 2009). The average globule sizes for the lotions are 3 μm or less and for the cream is about 10 μm. The globule size appeared to be inversely related to the permeation of octocrylene from the lotions and the cream (**Figure 3**), suggesting that smaller globules with larger surface area for interaction with the skin may facilitate skin permeation of UV-filters. However, due to the differences in the excipients used in these formulations (**Figure S2**), it cannot be concluded that the difference in globule size is the only reason for the differences observed in the skin absorption of octocrylene. Metamorphosis (Roberts et al., 2017) of the emulsions upon contact with the skin is a dynamic process which may also affect the release and permeation of active ingredients.

2.3 Skin permeation of various sunscreen ingredients

Sunscreen products evaluated in this study exhibited skin permeation of UV-filters. Some sunscreen products differ in the quantity of UV-filters and parabens (**Table S1**). To facilitate the comparison of permeation potential of these ingredients among various sunscreen products, the permeation results of each ingredient were dose-normalized based on the content of the

corresponding ingredient in A-lotion. Summary results in **Figure 3** and **Table S4** are cumulative permeation at each sampling time point from 4 donors. Cumulative permeation data of individual donors are shown in **Tables S5-S8**. **Table 1** is the rank order of skin absorption (permeation and retention) for all products based on the total amount observed at 24 h.

The results in **Figure 3a** and **Table 1** show that the permeation of avobenzone exhibits the following rank order: A-lotion ≈ B-spray ≥ cream ≥ A-spray ≥ B-lotion. At 3 h, the permeation of avobenzone was observed from the lotions and sprays but not from the cream. A-lotion exhibited significantly higher permeation of avobenzone than B-lotion at 3 h (***p<0.001), but the significance of the observation disappeared at 24 h. Octocrylene has a log$P$ value of 6.8 and is the most lipophilic UV-filter of those tested. The permeation of octocrylene exhibits the following rank order: A-lotion ≥ B-spray ≥ B-lotion ≥ A-spray > cream (**Table 1** and **Figure 3b**). The cream exhibited the lowest permeation of octocrylene at 3 and 6 h, but the significance of the observation disappeared at 24 h. This trend suggests that the cream (with larger globules of approximately 10 µm) may delay the permeation of octocrylene as compared to the lotions (with smaller globules of approximately 3 µm). The lotions with similar oil globule sizes were observed to have similar levels of skin permeation of octocrylene. Moreover, permeation of octocrylene from the lotions compared to B-spray was not significantly different.

Across all products, the total permeation of oxybenzone was up to 200-fold greater than avobenzone and octocrylene. The observed high *in vitro* permeation confirmed the predictions deduced from the physiochemical properties of the UV-filters (**Table S1**) and agreed with the published reports on high *in vivo* absorption of oxybenzone (Jiang et al., 1999). Permeation of oxybenzone between the two lotions was not significantly different (**Figure 3c**). However, both lotions were found to exhibit significantly higher permeation of oxybenzone than B-spray. The

results in **Table 1** show that the permeation of oxybenzone from various products exhibited the following rank order: B-lotion ≈ A-lotion ≈ A-spray > B-spray. Interestingly, with an infinite dose applied to the skin, *in vitro* permeation of oxybenzone was higher from the water-based A-spray and lotions than from the alcohol-based B-spray.

Ecamsule was only present in the cream and was found to permeate the skin over the course of 24 h in greater quantities than avobenzone and octocrylene (**Figure 3d**). Having a log*P* value of 1.4 and being majorly in the matrix of the emulsion (**Figure 1**) may facilitate skin permeation. Parabens were only found in the lotions and the cream and were used as positive controls for skin permeation. The results in **Figures 3e-f** showed that the permeation of both parabens was similar among all the products.

2.4 Comparative Results of Skin Retention

The summary results of all donors in **Figure 4a** and **Table S9** show that B-spray exhibited the highest skin retention of all the UV-filters compared to other sunscreen products. Skin retention of avobenzone and octocrylene from B-spray was found to be significantly higher than skin retention from the cream, probably due to formulation differences. Although B-spray exhibited the highest skin retention of oxybenzone among all formulations, the differences were not found statistically significant. The skin retention of methylparaben from A-lotion was found to be significantly higher than that from the B-lotion but not from the cream. Skin retention data of individual donors are shown in **Tables S10-S12**.

2.5 Rank order of sunscreen products

The rank order of skin permeation and retention of UV-filters and parabens in the studied sunscreen products is described in **Table 1**. Among all products, A-lotion has the highest permeation of avobenzone and octocrylene; B-spray has the highest skin retention of all the UV-filters. Notably, the trend of oxybenzone detected in the permeation sample is in a reversed sequence to that observed in the skin. B-spray has the highest skin retention of oxybenzone, but the lowest oxybenzone in the permeation samples as compared to other products. However, since the majority of oxybenzone was retained in the skin (54.4 $\mu g/cm^2$) rather than found in the skin permeation samples (7.1 $\mu g/cm^2$), skin retention of UV-filters predominates the overall results of the rank order. For emulsion sunscreens, A-lotion demonstrated the highest absorption of all ingredients. B-spray and A-lotion were selected for clinical MUsT study (Matta et al., 2019) due to B-lotion's withdrawal from the market.

As the first attempt of IVPT method optimization for sunscreen products, there are possible limitations in the current study that warrant further investigation of the methodologies. For example, because this study evaluated only marketed products with different formulations and excipients, the contributions of various formulation variables to the observed *in vitro* characteristics of the products cannot be clearly ruled out (Benson et al., 2005). A design of experiment (DOE) approach may be needed to closely evaluate the effect of an individual process or formulation variables on the performance of the final product (i.e. viscosity). Second, the IVPT study used split-thickness cadaver skin including the entire epidermal layers and partial dermis with a fixed total thickness. Further studies may be done with the skin of different

thickness for method optimization. It is worth noting that, different from *ex vivo* skin cultures and freshly excised post-operative human skin, cadaver skin may not have viable cells. The status of the cornified envelope, stratum corneum, and epidermal tight junctions among these skin models may be different from viable skin, and data variability may be higher when cadaver skin is used. Cautions should be exercised when choosing a suitable skin model for IVPT. We have demonstrated in a previous study that the cadaver skin, obtained from the same source as for this study, and the freshly excised viable human skin have comparable barrier functions (Yang et al., 2015). Third, a single application using an infinite dose of the sunscreen product was employed in this study to match with the total amount of sunscreen used in the clinical MUsT study. However, in-use conditions, such as single or repeated finite dose application of sunscreen (i.e. 2-10 mg/cm^2) may be employed to optimize the IVPT method, as finite dosing may produce different hydration and viscosity effects as compared to infinite dosing. Also, finite dosing may allow precise assessment of the absorption of UV-filters by recovery analysis (the quantitation of actives in each compartment, including the actives in the skin and removed by wiping). Forth, since the IVPT was exploratory for UV-filters and the primary objective was to assist product selection for MUsT studies, the sampling time points may have been less than the ideal sampling plan for IVPT of topical products. More frequent sampling could be implemented to obtain the entire *in vitro* flux profile of the UV-filters for comparison with *in vivo* PK profile. Fifth, this IVPT study was conducted using an average skin surface temperature of 32˚C; further testing with elevated temperature or in the presence of UV radiation could better mimic outdoor conditions. Moreover, this study utilized commercial static Franz diffusion cells to achieve the required sink conditions for all hydrophobic UV-filters. Choosing a static diffusion system over a dynamic flow through system such as PermeGear in-line cells was to maintain a detectable

concentration of UV-filters in the receptor solution by minimizing the receptor volume (SCCP, 2006). The challenge of using the static diffusion system with manual sampling was the lack of freedom to take samples as much as can do with the flow through system (with automated sampling capability). There were also reports about unstirred aqueous diffusion layers present in the receiver chambers of the Franz cells. Unstirred layers may lead to an underestimation in the actual extent of drug permeation (Miller and Kasting, 2012, Yousef et al., 2017). Therefore, a suitable receiver solution should be carefully selected to avoid unstirred aqueous layers by maintaining sink conditions (i.e. including 4% BSA in the receiver solution) and efficient stirring (i.e. at 600 rpm). Finally, this study was designed as a pilot to determine rank order trends; therefore, the design included only 4 chemical UV-filters in marketed sunscreen products. Other UV-filters with different physicochemical properties may be included in future studies with more sophisticated bioanalytical methods to overcome analytical challenges.

In conclusion, fit-for-purpose methodologies were used to evaluate the absorption potential and *in vitro* biopharmaceutical characteristics of various sunscreen products to predict product performance. The use of discriminatory IVPT accompanied with *in vitro* formulation characterization collectively provided the basis for the selection of products for an FDA-sponsored MUsT clinical pilot study (Matta et al., 2019). The IVPT method described in this study may also be used for product selection during early development stages for further *in vivo* safety evaluation (Adamson and Shinkai, 2020). Most importantly, the study provided a rank order reporting platform for IVPT results that can be further optimized to better enhance its predictability for *in vivo* absorption of the product.

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4. Materials and Methods

Description of materials and additional methods are in the Supplementary Material.

Preparation of skin samples for permeation studies:

Dermatomed human cadaver skin (from 4 female donors, 60-80 years of age, 250 µm average thigh skin thickness) was obtained from Science Care (Phoenix, AZ, USA) with written informed consent (IRB review is not needed as the definition of human subject pertains to living individuals). Circular skin samples were punched-out using a die cutter (18.5 mm in diameter) and gently cleaned with water. The individual skin thickness was measured using a caliper and recorded. The barrier integrity of the skin was tested by measuring trans-epidermal water loss (TEWL) using a vapometer (Delfin Technologies, Kuopio, Finland). Skin samples free of any visual physical damage and having a TEWL of less than 10 $g/cm^2 \cdot h$ were used in IVPT (Benech-Kieffer et al., 1997).

In vitro skin permeation test (IVPT)

In vitro skin permeation test of various sunscreen products was carried out using vertical Franz diffusion systems (PermeGear, Inc. Hellertown, PA). Each jacketed Franz diffusion cell (15 mm orifice diameter, 1.77 cm^2 exposure area, 12 mL receiver volume) was placed on the stirrer and the skin surface temperature was maintained at 32˚C. The receiver chamber was filled with PBS containing 4% BSA (*w/v*) (Freitas et al., 2015) and stirred constantly at 600 rpm. Prepared circular skin samples were sandwiched between donor and receiver chambers with stratum corneum (SC) facing the donor side. To obtain the maximum possible skin absorption, an infinite dose of 100 mg of sunscreen product (lotion or cream) was applied to the SC side of the skin. For

spray products, the solution was first sprayed in to a glass scintillation vial and then 120 μL (equivalent to 100 mg) of the solution was immediately applied to the skin surface (Matta et al., 2019). The experiment was carried out under non-occlusive conditions while the entire system was protected from light using aluminum foil. Aliquot skin permeation samples (100 μL) were collected from the receiver chamber at 0, 3, 6 and 24 h for analysis and 100 μL of fresh receiver solution was replenished into the receiver chamber. Permeation results obtained from individual donors were summarized in **Tables S5-S8**. Sunscreen ingredients retained in the skin samples were extracted using methanol for analysis. Skin rretention results obtained from individual donors were summarized in **Tables S10-S12**.

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5. Data Availability Statement

Datasets related to this article can be found at http://dx.doi.org/10.17632/hgj8kcygj2.1, an open-source online data repository hosted at Mendeley data.

6. Disclaimer and conflict of interest

This manuscript reflects the views of the authors and should not be construed to represent FDA's views or policies. The authors state no conflict of interest.

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Table 1. Rank order of mean cumulative skin permeation and retention of sunscreen ingredients over 24 h (rank 1 to 5 as highest to lowest skin permeation/retention)

Product Type	Rank order of ingredients permeated through cadaver skin (1→5: Highest → Lowest)					
	Avobenzone	Octocrylene	Oxybenzone	Ecamsule	Methylparaben	Propylparaben
B-lotion	5	3	**1 ***	-	**1**	**1**
A-lotion	**1**	**1**	2 $^{\#}$	-	2	3
A-spray	4	5	3 $^{\Delta}$	-	-	-
B-spray	2	2	4 $^{*,\#,\Delta}$	-	-	-
Cream	3	4	-	1	3	2
Statistical Difference	No	No	$^{*,\#}p<0.005$; $^{\Delta}p<0.05$	-	No	No
Product Type	**Rank order of amount of ingredients retained in cadaver skin* (1→5: Highest → Lowest)**					
	Avobenzone	Octocrylene	Oxybenzone	Ecamsule	Methylparaben	Propylparaben
B-lotion	4	4	4	-	3 $^{\Delta}$	2
A-lotion	3	3	3	-	**1** $^{\Delta}$	**1**
A-spray	2	2	2	-	-	-
B-spray	**1 ***	**1** $^{\Delta}$	**1**	-	-	-
Cream	5 *****	5 $^{\Delta}$	-	1	2	3
Statistical Difference	$^{*}p<0.005$	$^{\Delta}p<0.05$	No	-	$^{\Delta}p<0.05$	No

Note that the skin permeation and retention data was dose normalized based on the composition of the A-lotion. The skin retention data was also normalized based on 250 μm of skin thickness.

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Figures Legends:

Figure 1. Raman microscopy, mapping and multivariate analysis of globules and matrices observed in the semi-solid sunscreen products. **a**) Raman spectra of USP reference standards for all the UV-filters. **b**) Optical images obtained using 100× objective for the cream, A-lotion and B-lotion (left to right). **c**) Average Raman spectra of 30 spots each taken from either the matrix (red) or a globule (green) overlaid for comparison for the cream, A-lotion and B-lotion (left to right). Raman mapping and multivariate image analysis of the cream. **d**) 100× optical image of area selected for Raman mapping. **e**) MCR-ALS scores image calculated based on a 3-component system colored according to MCR-ALS loadings (**f**). Component 1: ecamsule, component 2: octocrylene / avobenzone, component 3: dimethicone. Scale bar = 25 µm.

Figure 2. Cryo-SEM characterization of the semisolid sunscreen products. SEM images of vitrified sunscreen products: **a**) cream, **b**) A-lotion, and **c**) B-lotion. Scale bars are 50 µm in the upper and 10 µm in the lower images. Histograms of the diameters calculated from the SEM images of sunscreen products were fitted with a log normal distribution (**d**). Mean globule diameter (µm) ± standard deviation (SD) for the sunscreen product (**d**-inset).

Figure 3. Skin permeation of UV-filters and parabens after dose-normalizing the amount of ingredients according to the composition in the A-lotion. **a)** avobenzone, **b)** octocrylene, **c)** oxybenzone, **d)** ecamsule, **e)** methylparaben, and **f)** propylparaben. Data expressed as mean (ng/cm^2 skin) ± standard errors (SE). *p<0.05, **p<0.005, and ***p<0.001.

Figure 4. Skin retention of UV-filters and parabens after 24 h of IVPT. Data expressed as mean skin retention ($\mu g/cm^2$) ± standard errors (SE) of **a)** UV-filters and **b)** parabens. Dose and skin thickness were normalized according to the composition in the A-lotion and an average skin thickness of 250 µm. *p<0.05 and **p<0.005.

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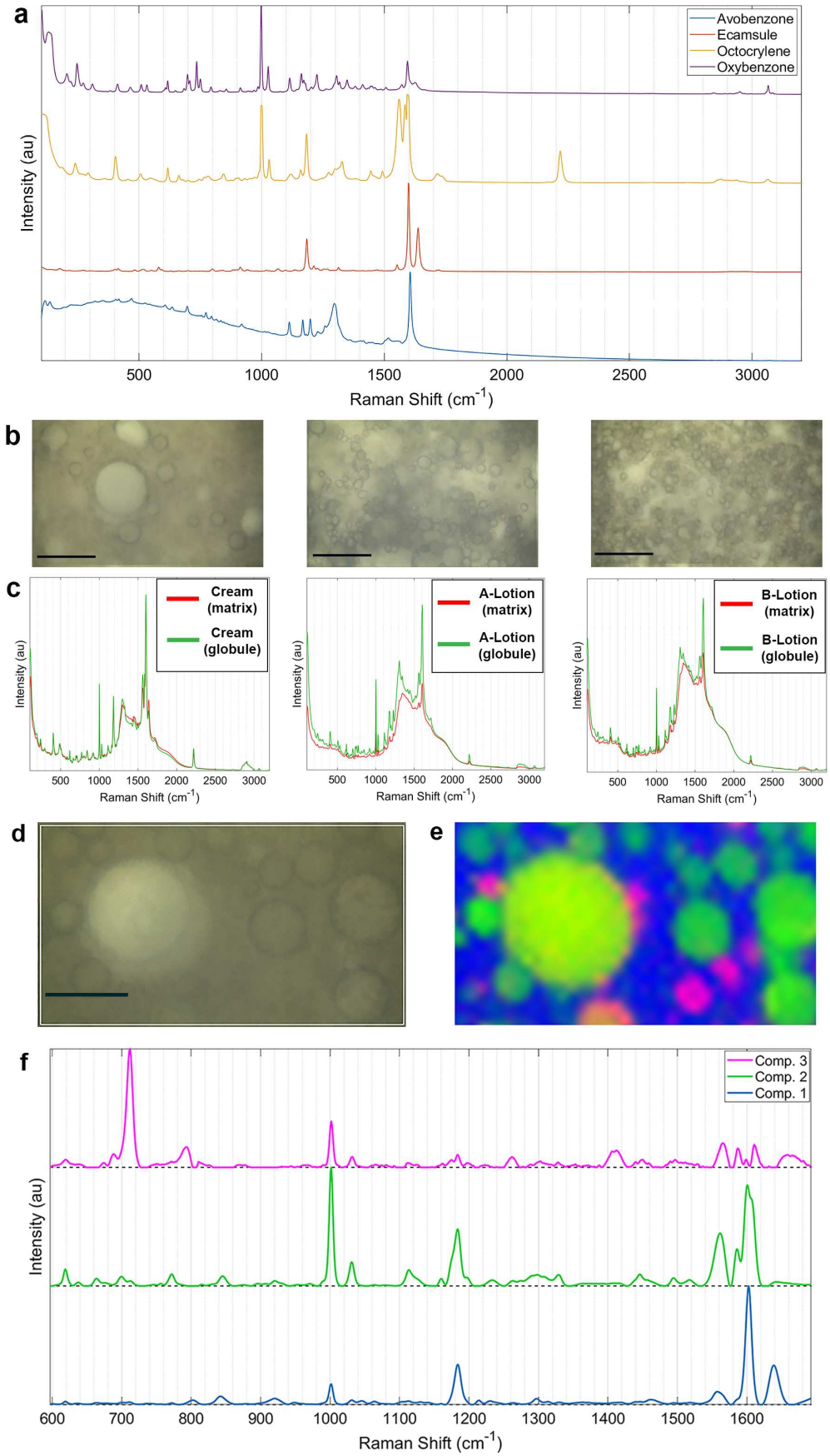
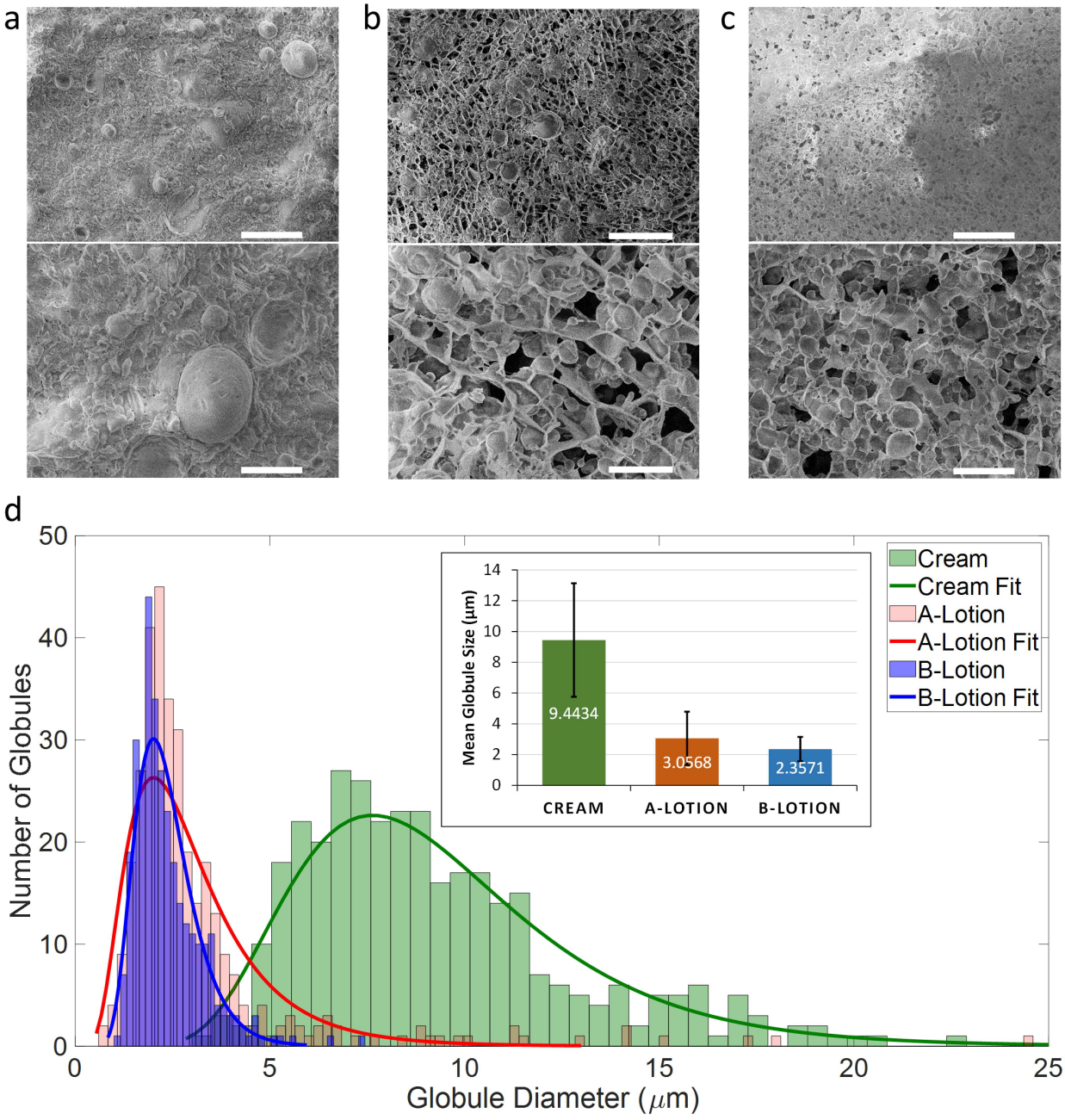
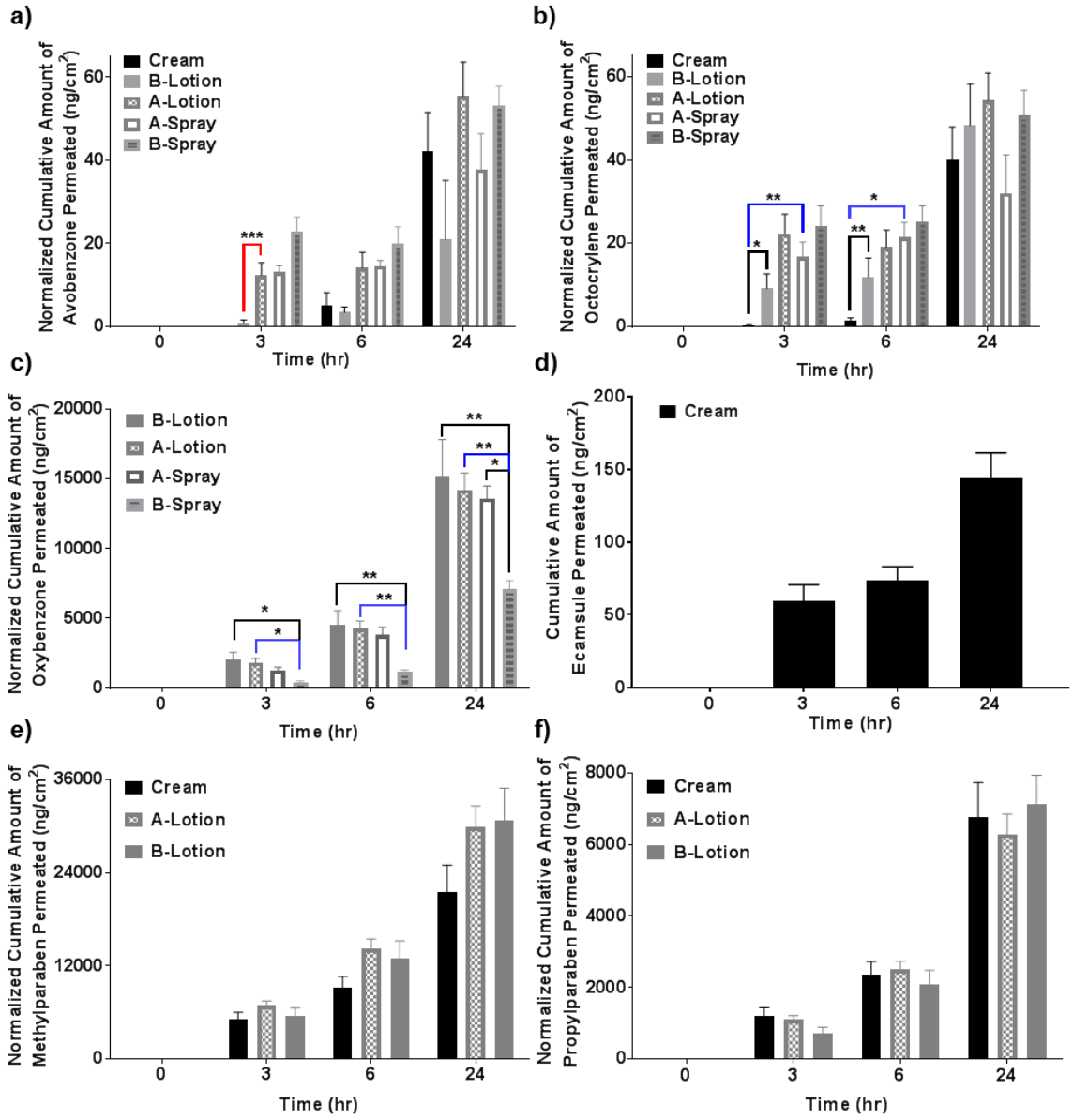
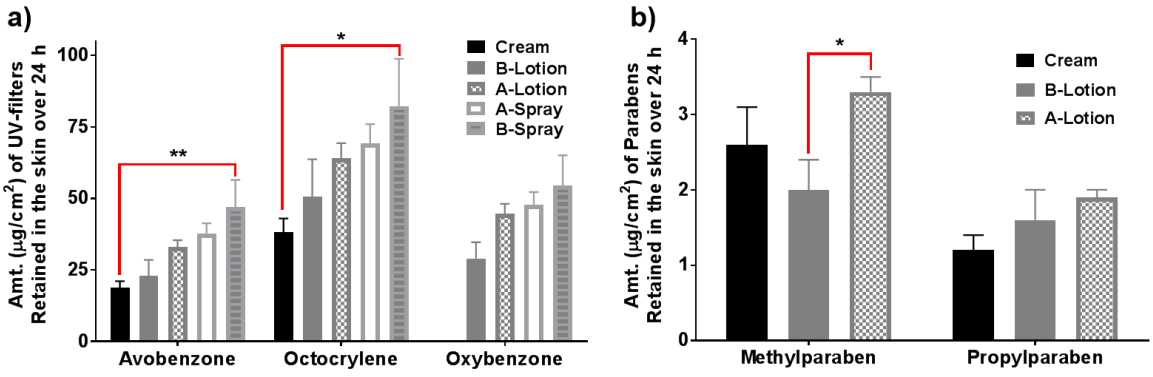

a
Avobenzone
Ecamsule
Octocrylene
Oxybenzone
Intensity (au)
500
1000
1500
2000
2500
3000
Raman Shift (cm-1)
b
c
Cream (matrix)
Cream (globule)
A-Lotion (matrix)
A-Lotion (globule)
B-Lotion (matrix)
B-Lotion (globule)
Intensity (au)
Raman Shift (cm-1)
d
e
f
Comp. 3
Comp. 2
Comp. 1
Intensity (au)
600
700
800
900
1000
1100
1200
1300
1400
1500
1600
Raman Shift (cm-1)


a
b
c
d
Number of Globules
Globule Diameter (μm)
Cream
Cream Fit
A-Lotion
A-Lotion Fit
B-Lotion
B-Lotion Fit
Mean Globule Size (μm)
9.4434
3.0568
2.3571
CREAM
A-LOTION
B-LOTION


a)
Normalized Cumulative Amount of Avobenzone Permeated (ng/cm2)
Cream
B-Lotion
A-Lotion
A-Spray
B-Spray
Time (hr)
b)
Normalized Cumulative Amount of Octocrylene Permeated (ng/cm2)
Cream
B-Lotion
A-Lotion
A-Spray
B-Spray
Time (hr)
c)
Normalized Cumulative Amount of Oxybenzone Permeated (ng/cm2)
B-Lotion
A-Lotion
A-Spray
B-Spray
Time (hr)
d)
Cumulative Amount of Ecamsule Permeated (ng/cm2)
Cream
Time (hr)
e)
Normalized Cumulative Amount of Methylparaben Permeated (ng/cm2)
Cream
A-Lotion
B-Lotion
Time (hr)
f)
Normalized Cumulative Amount of Propylparaben Permeated (ng/cm2)
Cream
A-Lotion
B-Lotion
Time (hr)



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