applied sciences

MDPI

Article

Incorporation of UV Filters into Oil-in-Water Emulsions—Release and Permeability Characteristics

Anna Olejnik [1,2] and Joanna Goscianska [1,*]

[1] Department of Chemical Technology, Faculty of Chemistry, Adam Mickiewicz University, Uniwersytetu Poznańskiego 8, 61-614 Poznań, Poland; anna.olejnik@amu.edu.pl
[2] Centre for Advanced Technologies, Adam Mickiewicz University, Uniwersytetu Poznańskiego 10, 61-614 Poznań, Poland
* Correspondence: asiagosc@amu.edu.pl

Abstract: Unlike in many countries, in the USA, UV filters are treated as drugs and strictly regulated by the Food and Drug Administration. So far, 17 physical and chemical sunscreen agents were approved there to protect against the harmful effects of UV irradiation. In the European Union, access to UV filters is much larger, which gives manufacturers more options to create new sunscreen products in the form of lotions, sprays, oils, creams, gels, pastes, and sticks. Recently, concerns have been raised about the potential unfavorable effects of some UV filters that can penetrate the skin and enter into the systematic circulation. In this study, we prepared oil-in-water emulsions containing two commonly applied sunscreen agents, avobenzone and octyl methoxycinnamate. The formulations were characterized by a high stability at room temperature and a pH in the range of 6.02–6.11. The processes of sunscreen agent release and permeation were performed in a receptor fluid with a pH 5.8 using Strat-M and cellulose membranes to mimic the skin. It was proved that octyl methoxycinnamate exhibited different liberation and permeation patterns than avobenzone, mostly due to its higher lipophilicity. Both processes were also influenced by the type of membrane applied. The liberation of UV filters to the receptor fluid via the cellulose membrane depended on their concentration in the emulsion. As the amount of sunscreen agent in the formulation increases, more of its molecules diffuse to the receiving medium after 48 h. The permeation of the UV filters through the Strat-M membrane occurs at a very low level, 2% for octyl methoxycinnamate and 0.3% for avobenzone, which supports the safety and efficacy of the topical formulations obtained.

Keywords: butyl methoxydibenzoylmethane; octinoxate; Franz cell; artificial membranes; sunscreen agents; colloidal systems

Citation: Olejnik, A.; Goscianska, J. Incorporation of UV Filters into Oil-in-Water Emulsions—Release and Permeability Characteristics. *Appl. Sci.* **2023**, *13*, 7674. https://doi.org/10.3390/app13137674

Academic Editors: Gianpiero Calabrese and Antonia Mancuso

Received: 11 June 2023
Revised: 25 June 2023
Accepted: 26 June 2023
Published: 28 June 2023

1. Introduction

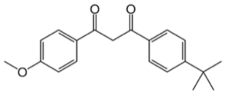
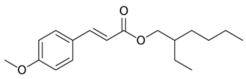
UV filters are a group of compounds, which protect the skin from ultraviolet light that can cause redness, burn, photoaging, and cancer [1]. They can be divided into inorganic (physical) and organic (chemical) agents [2]. UV blockers are sunscreen formulations' components and protect against harmful radiation by reflecting, scattering, or absorbing UV rays [3–5]. Depending on the type of photoblocker, the mode of their action is different. Inorganic filters usually reflect or scatter ultraviolet radiation via an optical mechanism [6,7]. In turn, organic UV blockers absorb the light that implicates chemical changes in the molecules, such as isomerization. These ultraviolet filters can also release the incident energy as heat and emit radiation at a higher wavelength [6]. In the USA, sunscreen agents are treated as over-the-counter drugs and are subjected to the regulation of the Food and Drug Administration (FDA) [8]. The FDA ensures that UV filters meet safety, quality, and efficacy standards. The availability of novel sunscreen agents in the USA is limited mainly due to a more complex and long-term approval process than in the European Union [9]. Lately, sunscreen agents have gained concerns due to reports in which it was proved that

some UV filters were photounstable, undergo photodegradation upon irradiation, and can cause allergies and toxic reactions, as well as penetrating the stratum corneum [10]. They were detected in plasma, urine [11], and even in human milk samples [12]. It was also reported that some UV filters can act as endocrine disruptors [13]. Therefore, the ideal sunscreen formulation should ensure skin accumulation of a UV filter, creating a stable film on its surface with negligible permeation to the systematic circulation [14]. The effectiveness of sunscreen agents depends on their ability to remain on the skin surface after the application of the formulation. UV filters should not permeate into the deeper layers of the skin. The formulation type may influence the safety and efficacy of sunscreen agents. In this study, two commonly applied sunscreen agents were selected: avobenzone (butyl methoxydibenzoylmethane-Avo), which provides protection against UVA and octyl methoxycinnamate (ethylhexyl methoxycinnamate-OMC), used as a UVB absorber [15]. These UV filters are components of sunscreen formulations, such as lotions, sprays, and other topical products, which protect against UV light. They are approved by regulatory authorities in the USA, Europe, Japan, and Australia [16]. However, it has been established that avobenzone is not photostable [17]; therefore, its photodegradation products may cause photoallergies [18]. To overcome this problem octocrylene is usually added to sunscreen formulations [19]. In turn, OMC is the most widely applied lipophilic UVB filter in cosmetic formulations because it exhibits the ability to impair water resistance in the final sunscreen product [20]. When octyl methoxycinnamate is exposed to sunlight, it is subjected to photoisomerization between the *cis*-(Z) and *trans*-(E) isomers [20]. The chemical structure and geometric properties of both UV filters are presented in Table 1. Ates et al. created a theoretical approach that enables the selection of molecules with a high skin permeability [21]. The following criteria were considered: the molecular weight should be lower than 180 Da; the melting point below 100 °C; log K_{ow} higher than 0.3; and topological polar surface lower than 40 $Å^2$. It was suggested that if the molecule follows at least two of these criteria, it will exhibit a high skin permeation. Based on these assumptions and considering the data presented in Table 1, both Avo and OMC should be able to permeate through human skin. However, Montenegro et al. proved that avobenzone exhibited a low skin permeability both in single and repeated applications [22]. The rate-limiting step of Avo diffusion was the release from the vehicle. In other studies, Montenegro et al. analyzed the effects of different types of emulsifiers on the permeation through the skin of the two above-mentioned sunscreen agents from o/w emulsion [23]. The results have revealed that the emulsifying system has a significant effect on the UV filter permeation from topical formulations so the vehicle for sunscreen agents should be selected carefully. Gupta et al. confirmed that penetration and stratum corneum retention of OMC were dependent on the type of formulation used [14]. Recent studies have indicated that avobenzone and octyl methoxycinnamate are photochemically unstable and their absorption properties are reduced due to exposure to sunlight [24,25]. Therefore, UV filters were entrapped in different materials to increase their photostability, sun protection, and to reduce potential skin permeation. So far, ordered mesoporous silica SBA-15 has been used to decrease the transdermal permeation of Avo and OMC [26]. It was reported that mesoporous silica containing Avo minimized the possible toxicity induced by percutaneous penetration [27]. Additionally, other inorganic vehicles, such as hydrotalcites and zeolites were also tested to increase the photostability and to prevent OMC absorption through the skin [20,28,29]. Jimenez et al. found that the incorporation of encapsulated octyl methoxycinnamate into the formulations reduced the accumulation of the UV filter in the skin [30]. The decrease in the penetration of OMC was achieved when it was introduced to solid lipid microspheres [31]. Scalia et al. reported that the loading of OMC and Avo into lipid microparticles reduced the percutaneous penetration of both UV filters [32]. In turn, Andreani et al. created a formulation consisting of hybrid lipid-silica nanoparticles with OMC incorporated into the hydrogel [33].

The aim of our research was the assessment of in vitro skin release and permeation of avobenzone (Avo) and octyl methoxycinnamate (OMC) from an oil-in-water emulsion.

Strat-M and cellulose membranes were applied to mimic the skin barrier. Prior to the release experiments, the sunscreen formulations obtained were characterized in terms of physicochemical parameters and stability.

Table 1. Physicochemical and geometric properties of avobenzone (Avo) and octyl methoxycinnamate (OMC) (Spartan '18. Version 1.4.5. 29 June 2020).

UV Filter	Structure	State of Matter	MW (g/mol)	Area (Å^2)	Volume (Å^3)	Topological Polar Surface Area (Å^2)	Log K_{ow} [1]	MP (°C)
Avo		solid	310	360.12	342.12	43.4	4.51	83.5
OMC		liquid	290	367.44	334.87	35.5	6.10	−68.3

[1] log partition coefficient octanol/water.

2. Materials and Methods

2.1. Preparation of Emulsions Containing UV Filters

Four oil-in-water emulsions with UV filters were obtained: two contained avobenzone in 0.5 and 2.0% *w*/*w* and two others consisted of octyl methoxycinnamate in 0.5% and 2.0% *w*/*w*. Additionally, as a reference, a formulation without sunscreen agents was prepared. The ingredients of the sunscreen formulations are collected in Table 2.

Table 2. Components of oil-in-water emulsions.

Ingredients	E (% *w*/*w*)	$E_{0.5\%Avo}$ (% *w*/*w*)	$E_{2\%Avo}$ (% *w*/*w*)	$E_{0.5\%OMC}$ (% *w*/*w*)	$E_{2\%OMC}$ (% *w*/*w*)
Water	69.3	68.8	67.3	68.8	67.3
Glycerin	7.5	7.5	7.5	7.5	7.5
Xanthan gum	0.3	0.3	0.3	0.3	0.3
Glycerol stearate	2.0	2.0	2.0	2.0	2.0
Polyglyceryl-3 metylglucose distearate	2.0	2.0	2.0	2.0	2.0
Cetyl alcohol	3.0	3.0	3.0	3.0	3.0
Shea butter	7.5	7.5	7.5	7.5	7.5
Vegetable oil	7.5	7.5	7.5	7.5	7.5
Avo/OMC	-	0.5	2.0	0.5	2.0
Phenoxyethanol	0.9	0.9	0.9	0.9	0.9

In the first step, the aqueous phase was prepared by dissolving the xanthan gum in glycerin. Next, an appropriate amount of water was added to this mixture. Concomitantly, the ingredients of the oil phase (glycerol stearate, polyglyceryl-3 metylglucose distearate, cetyl alcohol, shea butter, and vegetable oil) were weighed and heated to 70 °C. Avobenzone or octyl methoxycinnamate was introduced to the oil phase. Then, two phases were mixed and homogenized by a homogenizer (SilentCrusher M, Heidolph, Schwabach, Germany). After cooling the formulations, phenoxyethanol, used as a preservative, was added to all the emulsions. The formulations obtained were denoted as E (emulsion without sunscreen agents), $E_{0.5\%Avo}$, $E_{2\%Avo}$, $E_{0.5\%OMC}$, and $E_{2\%OMC}$.

2.2. Physicochemical Characterization of Emulsions

2.2.1. Measurements of pH

The pH value of the emulsions was measured in triplicate at RT using a pH-meter (Aqualytic, Dortmund, Germany).

2.2.2. Stability Studies

Centrifugation Test

The stability of the emulsions was evaluated by centrifugation at 3500 rpm for 5 min (MPW 56 Centrifuge, MPW Med. Instruments, Warsaw, Poland), and the phase separation was tested.

Zeta Potential

The electrokinetic properties of the emulsions were determined in distilled water using a Zetasizer Nano ZS (Malvern Instruments Ltd., Malvern, UK).

Multiple Light Scattering

The third stability test of the emulsions was carried out using Multiscan MS 20 (Data-Physics, Filderstadt, Germany) directly after their preparation and at different time intervals for 35 days at room temperature.

2.2.3. Particle Size Distribution

The particle size distribution of the emulsions was measured using a Mastersizer 3000 (Malvern Instrument Ltd., Malvern, UK) with a wet dispersion unit. Before the measurements, the refractive index of each sample was determined. The data are presented as percentages of d (0.1), d (0.5), and d (0.9):

- d (0.1) (μm)—10% of the particles have a size smaller than the measured value,
- d (0.5) (μm) is the median where 50% of the particles have a size above the measured value and the size of 50% is below the data obtained,
- d (0.9) (μm)—90% of the particles have a size smaller than the results obtained [34].

In addition, D [3,2]—the surface-weighted mean (Sauter mean) estimating the mean size of a given particle distribution was provided [35].

2.2.4. Optical Microscopy

The optical microscope (VHX-7000, Keyence, Osaka, Japan) was used to observe the droplet size of the emulsions.

2.3. Release Studies of UV Filters from Emulsions

The release studies of avobenzone and octyl methoxycinnamate from the emulsions were carried out through dialysis tubing cellulose membranes (Sigma Aldrich, St. Louis, MO, USA) in 200 mL of receptor medium mimicking the pH of the skin (mixture of phosphate buffer with pH 5.8 and ethanol in the ratio of 1:1) maintained at 32 °C ± 0.50 °C. The samples were withdrawn at a certain time (0.5; 1; 2; 3; 6; 12; 24; 48 h) and variations in the concentration of the Avo and OMC were registered using a UV-Vis spectrophotometer (Cary 60, Agilent, Santa Clara, CA, USA) at wavelengths of 361 nm and 311 nm, respectively. The release results were fitted to different kinetic models, such as zero-order ($F_t = k_0 t$), first-order ($F_t = 1 - e^{-kt}$), Higuchi's model ($F_t = k_H \sqrt{t}$), Korsmeyer–Peppas model ($F = (M_t/M) = k_{KP} t^n$), and the Hixson–Crowell model ($\sqrt[3]{F_0} - \sqrt[3]{F_t} = k_{HC} t$), where F_t is the fraction of Avo/OMC released into the receptor medium over time, t (h); F_0 is the initial amount (mg) of the UV filter in emulsion; and k_0, k, k_H, k_{KP}, k_{HC} are the release constants of the particular kinetic models [36]. The correlation coefficient (R^2) established which kinetic model follows a certain release profile.

2.4. Permeation Studies of UV Filters

The permeation study of both the Avo and OMC from emulsions through a Strat-M membrane (Merck Millipore, Burlington, MA, USA) was performed using a vertical Franz cell (PermeGear, Inc., Hellertown, PA, USA). The receptor cells were filled with 15 mL of medium consisting of phosphate buffer with pH 5.8 and ethanol in the ratio of 1:1, which were allowed to equilibrate at 32.5 °C under magnetic stirring. The Strat-M membrane was pre-equilibrated in the receptor fluid at RT for 30 min. The permeation of the UV filters was determined at different time intervals (0.5; 1; 1.5; 2; 2.5; 3; 3.5; 4; 5; 6; 24; 32; 48 h) by measuring the concentration of the Avo and OMC in the receiving solution using UV-Vis spectrophotometry at wavelengths of 361 nm and 311 nm, respectively. The cumulative amount (mg/cm^2) of sunscreen agents that permeated through the Strat-M was calculated considering the standard calibration curve of each UV filter and the effective diffusion area of the Franz cell (3.14 cm^2). The results obtained were plotted as a function of time.

3. Results and Discussion

3.1. Physicochemical Characterization of Oil-in-Water Emulsions with and without UV Filters

All the prepared samples were oil-in-water emulsions, containing mostly an aqueous phase (67.3–69.3% by weight). The maintenance of the proper pH of the skin is crucial. The surface of a healthy stratum corneum is acidic, in the range of pH 4.5 to 6.0 [37]. However, both endogenous (skin moisture, sweat, sebum, age, and genetic predispositions) and exogenous (detergents, cosmetic products, and topical antibiotics) factors may affect the pH value of the skin surface [38]. Topically applied cosmetics may contribute to preserving appropriate skin conditions. Therefore, the selection of skin care products should be considered carefully. As the sunscreen formulations are intended to be applied topically on the skin surface, the pH values of each emulsion were analyzed. The results are gathered in Table 3. The pH values of the formulations range from 6.02 to 6.11, which is acceptable for cosmetic products. The addition of both UV filters only slightly increased the pH value of the emulsions. It should be stressed that the most problematic, for technologists, are sunscreen formulations containing zinc oxide because the pH can be shifted toward 7.5, which reduces the number of preservatives possible to be applied to the product [39]. In the case of the emulsions obtained in this study, this issue was not detected. The stability of the prepared formulations was assessed using a centrifugation test, a multiple light scattering method, and by the determination of the zeta potential value. No phase separation was observed in any of the samples tested after centrifugation.

Table 3. Physicochemical characterization of emulsions.

Sample	pH	Zeta Potential (mV)	Refractive Index
E	6.02 ± 0.04	−79.0 ± 1.3	1.3590
$E_{0.5\%Avo}$	6.04 ± 0.06	−75.1 ± 1.9	1.3543
$E_{2\%Avo}$	6.06 ± 0.08	−73.0 ± 1.5	1.3555
$E_{0.5\%OMC}$	6.09 ± 0.07	−57.1 ± 2.0	1.3580
$E_{2\%OMC}$	6.11 ± 0.10	−54.2 ± 1.8	1.3567

The zeta potential values of all five formulations exceeded ±30 mV, which proved their high degree of stability. High negative or positive electrokinetic values give information that the particles in the suspensions tend to repel and thus the flocculation process is prevented [40]. It was found that the addition of UV filters to emulsions decreased the zeta potential value compared to the emulsion without the sunscreen agent; however, it remained at the proper high level. The stability of the formulations was also assessed using multiple light scattering. This method allows to characterize the samples without dilution [41]. Moreover, it is possible to detect any changes occurring in the sample much faster than by the naked eye. Therefore, the aging tests can be shortened significantly [42].

As the results of the measurements, the transmission and backscattering (BS) profiles versus the height of the sample were registered and the exemplary graphs are presented in Figure 1. As the emulsions were opaque systems the variation in backscattering was only considered. It should be highlighted that for stable products all backscattering profiles will overlap over time. In turn, for unstable samples, the variations in backscattering profiles will be visible. Furthermore, no changes in particle size occurs if the BS profiles do not exceed 2% [43]. When changes are higher than 10%, the formulation is treated as unstable [44].

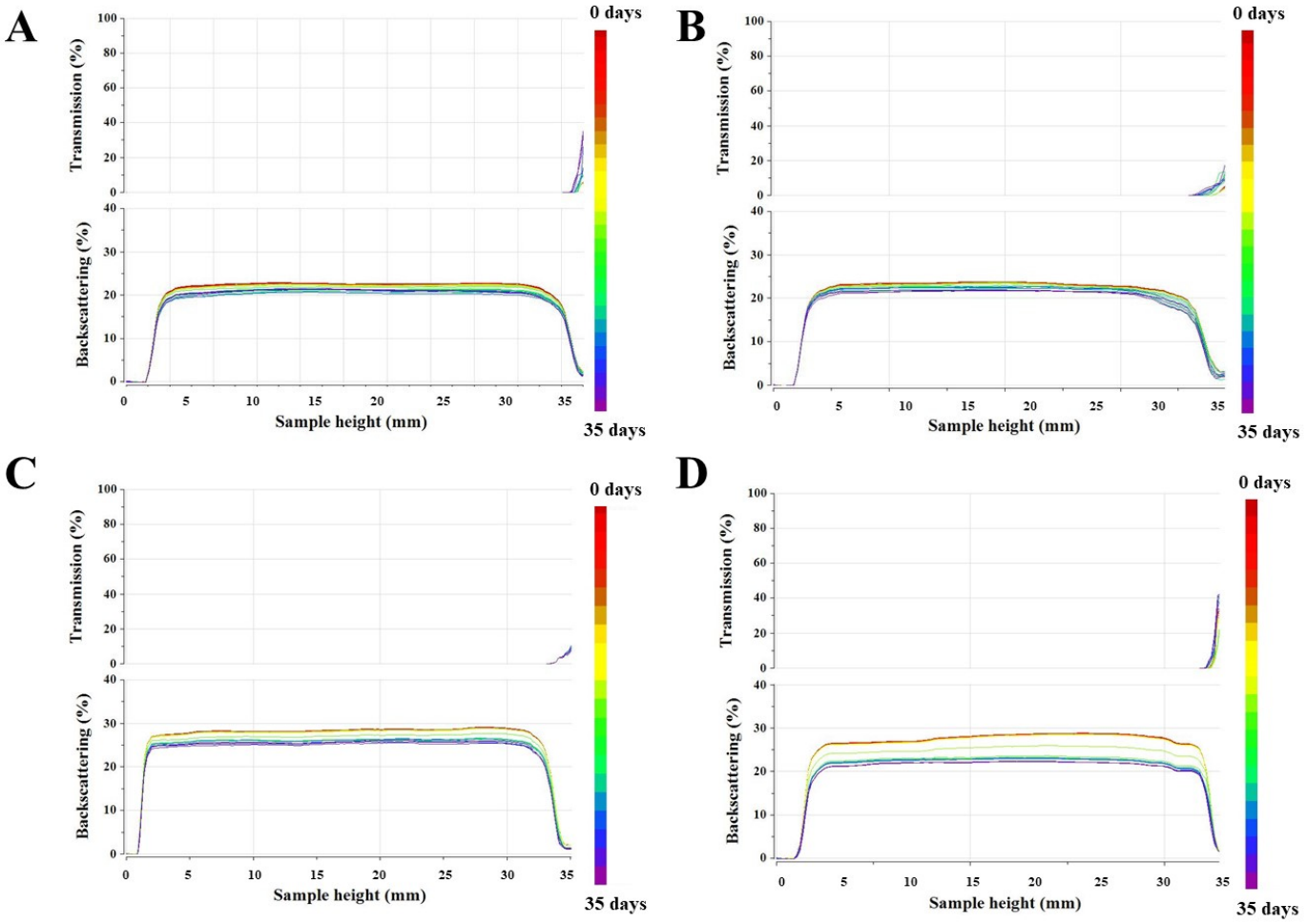


Figure 1. Transmission and backscattering profiles of emulsions without UV filter (**A**) and with avobenzone $E_{0.5\%Avo}$ (**B**), $E_{2\%Avo}$ (**C**), and octyl methoxycinnamate $E_{2\%OMC}$ (**D**).

It can be observed in Figure 1A,B that the BS profiles of samples E and $E_{0.5\%Avo}$ remained almost unchanged during the 35 days so it confirms that the 0.5% of avobenzone did not affect the stability of the emulsion. Whereas for $E_{2\%Avo}$ a slight variation in the delta BS (2.8%) was detected. Much greater changes in the backscattering profiles were noticed when octyl methoxycinnamate was added to the formulation. These results are in accordance with the zeta potential measurements (Table 3). To better visualize the changes in the samples, the stability index was calculated. It takes into consideration all the destabilization processes occurring in the tested product [45] and enabled to compare the stability of formulations. In Figure 2 changes in the stability index over time are depicted. The variations in the samples decreased in the following order $E_{2\%OMC} > E_{0.5\%OMC} > E_{2\%Avo} > E_{0.5\%Avo} > E$.

In the next step, the refractive indices (R_f) of the formulations were measured. Based on the results presented in Table 3, the values of R_f ranged from 1.3543 to 1.3590, which is typical for oil-in-water emulsions [46]. These data were then applied to determine the particle size distribution of the topical formulations. The results are depicted in Figure 3

and Table 4. It was proved that the addition of UV filters did not significantly change the particle size distribution of the samples compared to the emulsion without sunscreen agents. The particle sizes ranged from 0.3 to 100 µm. Bimodal particle size distribution with one predominant peak (average size around 1 µm) was detected for E, $E_{0.5\%Avo}$, $E_{2\%Avo}$, and $E_{2\%OMC}$. Whereas for $E_{0.5\%OMC}$ the predominant peak was shifted towards slightly larger particle sizes. The slight differences in particle size distribution between the formulations with avobenzone and without this UV filter may be related to the time of the homogenization process. The emulsion containing 2% of avobenzone was homogenized much longer compared to $E_{0.5\%Avo}$ and E, to disperse completely the UV filter. Therefore, the particle size of $E_{2\%Avo}$ was smaller than two other formulations. It is generally known that the increase in the duration of homogenization can lead to the reduction in particle size [47]. In turn, when a smaller amount of UV filter ($E_{0.5\%Avo}$) was used, the action time of the dispersion tool was the same as for the formulation without Avo. Therefore, the particle sizes of these two emulsions were similar. Additionally, the analyses were performed with and without ultrasound treatment to observe if potential aggregates that occurred in the emulsions can be broken down. All the formulations had bimodal particle size distribution regardless of the condition of the measurement. Ultrasound treatment reduced only slightly the size of the aggregates of the oil-in-water emulsions. The effect of ultrasound treatment on the particle size distribution of each sample was presented in Supporting Information (Figure S1). The biggest changes in the average particle size of samples D [3,2] were noted for $E_{2\%OMC}$. These results are in line with the data obtained by the zeta potential measurements and multiple light scattering, where variation in the stability index for $E_{2\%OMC}$ was the most noticeable.

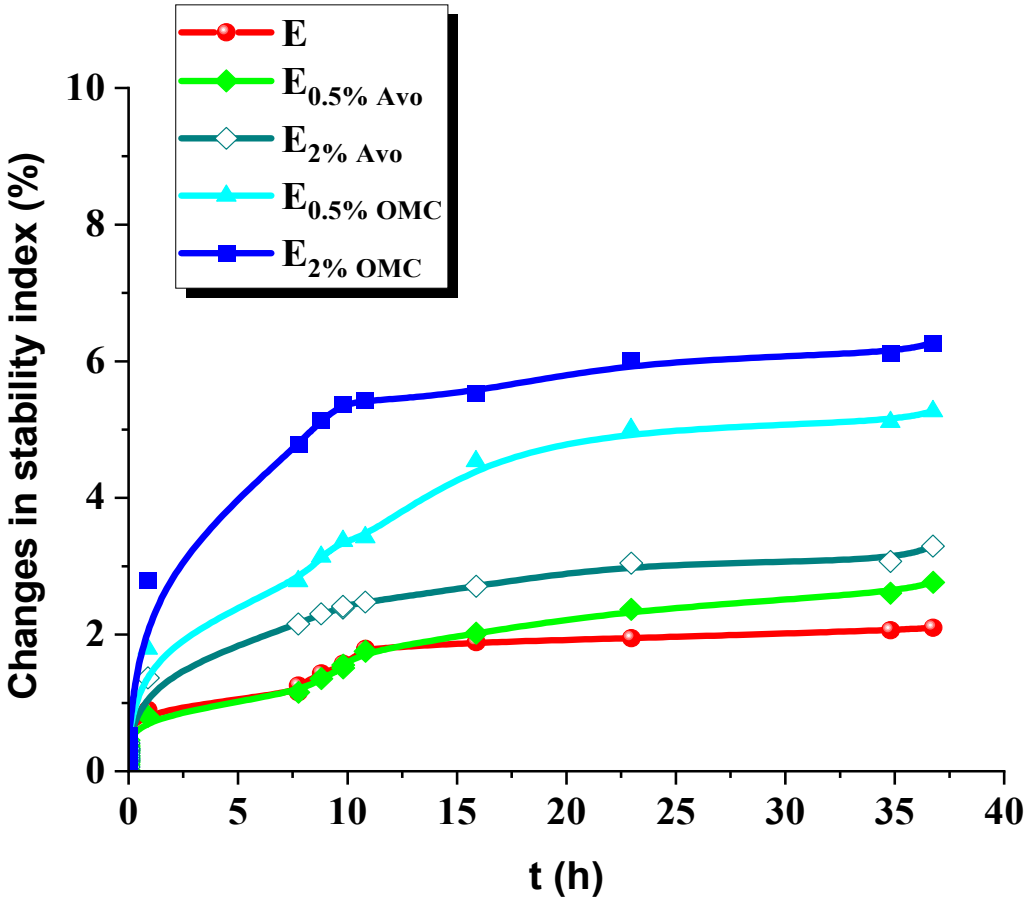


Figure 2. Changes in the stability index of formulations obtained.

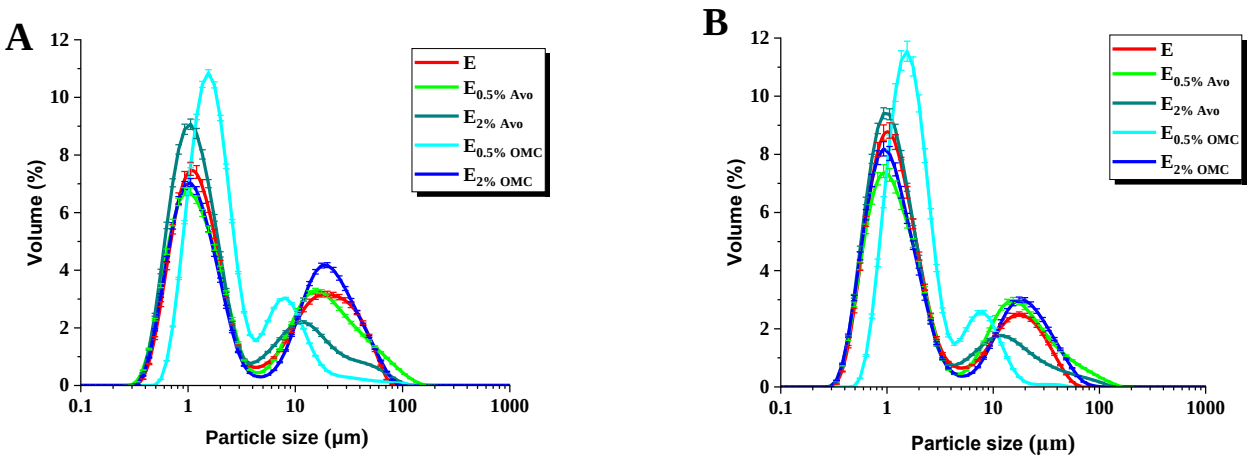


Figure 3. Particle size distributions of topical formulations measured without (**A**) and with the use of ultrasounds (**B**).

Table 4. Parameters determined based on the particle size distribution measurements of emulsions with and without UV filters.

Emulsion	E	$E_{0.5\%Avo}$	$E_{2\%Avo}$	$E_{0.5\%OMC}$	$E_{2\%OMC}$
D [3,2]	1.570 ± 0.008 µm	1.620 ± 0.014 µm	1.300 ± 0.001 µm	1.790 ± 0.001 µm	1.640 ± 0.016 µm
d(0.1)	0.671 ± 0.002 µm	0.716 ± 0.001 µm	0.652 ± 0.002 µm	0.983 ± 0.001µm	0.696 ± 0.026 µm
d(0.5)	1.850 ± 0.011 µm	1.780 ± 0.023 µm	1.370 ± 0.006 µm	1.850 ± 0.001 µm	1.890 ± 0.203 µm
d(0.9)	33.000 ± 0.153 µm	30.300 ± 1.535 µm	16.500 ± 1.170 µm	9.340 ± 0.045 µm	31.300 ± 1.077 µm
Ultrasound treatment					
D [3,2]	1.400 ± 0.088 µm	1.350 ± 0.083 µm	1.190 ± 0.082 µm	1.660 ± 0.016 µm	1.310 ± 0.108µm
d(0.1)	0.630 ± 0.021 µm	0.641 ± 0.026 µm	0.614 ± 0.019 µm	0.946 ± 0.007 µm	0.617 ± 0.036 µm
d(0.5)	1.570 ± 0.145 µm	1.370 ± 0.097 µm	1.250 ± 0.076 µm	1.730 ± 0.024 µm	1.400 ± 0.206 µm
d(0.9)	26.400 ± 2.533 µm	19.400 ± 2.146 µm	14.300 ± 1.543 µm	7.280 ± 0.446 µm	24.200 ± 1.720 µm

The effect of sunscreen agent addition to the oil-in-water emulsions was also studied by an optical microscope. It is a tool that enables the observation of any first signs of instabilities in the formulations [48]. In Figure 4, the images of all the oil-in-water emulsions prepared are displayed. No significant differences in droplet sizes between all the samples containing Avo and OMC were detected. In order to better visualize the similarity between the formulations, the diagrams presenting the % contribution of droplet size of the formulations E, $E_{0.5\%Avo}$, $E_{2\%Avo}$, $E_{0.5\%OMC}$, $E_{2\%OMC}$ are presented in Supporting Information (Figure S2). The data are consistent with the results obtained by laser diffraction and multiple light scattering.

3.2. Release and Permeation of UV Filters from Oil-in-Water Emulsions

As it was proved that the formulations were stable, and their particle size distributions were similar to each other, the release and permeation studies of avobenzone and octyl methoxycinnamate from o/w emulsions were carried out. Wester et al. suggested that the initial stage of percutaneous absorption of the active compound is related to its release from the formulation [49]. Consequently, in the first step, the release studies of UV filters from emulsions through the cellulose membrane were performed. The UV spectra of each sunscreen agent (Figure 5) were registered to determine the wavelength corresponding to the maximum absorbance characteristic for both the compounds in the receptor fluid selected for the release studies. The maximum absorbance (λ_{max}) of avobenzone was recorded at 265 nm and 361 nm, which corresponds to the keto and enol forms, respectively [50]. In

turn, in OMC, the benzene ring is substituted with 2-ethylhexyl propenoate ester group, acting as an electron acceptor, and methoxyl group in the para position is playing the role of an electron donor [51]. Therefore, the extended delocalization of electrons occurs in the OMC molecule. The λ_{max} for OMC was registered at 311 nm. The octyl methoxycinnamate protects against UVB, while avobenzone is a UVA sunscreen agent (Figure 5).

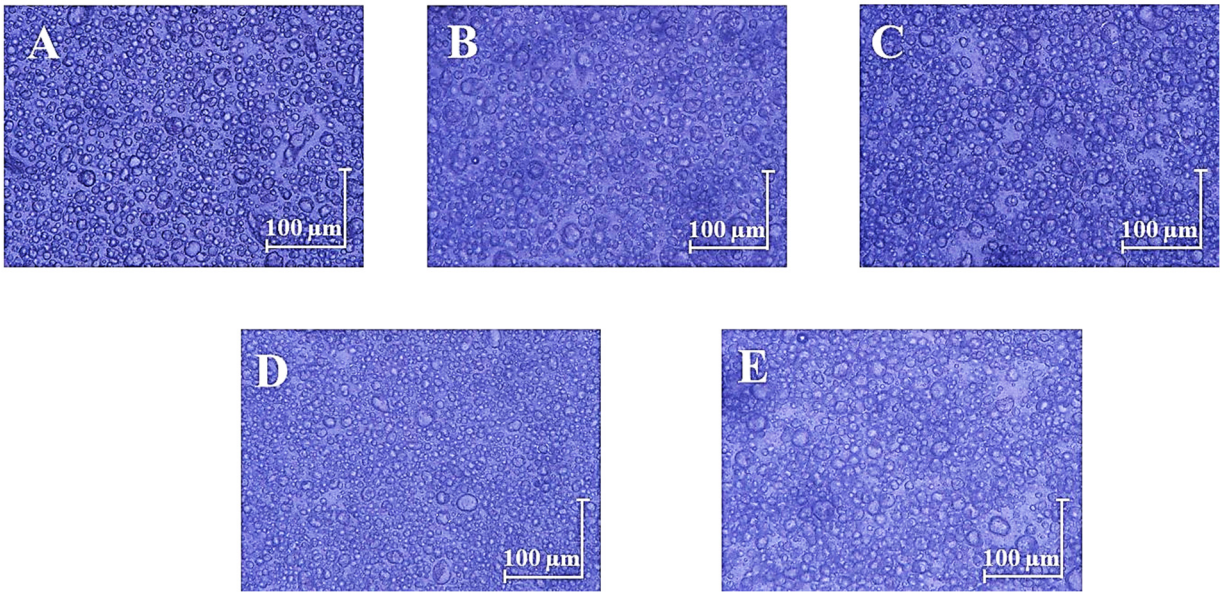


Figure 4. Optical microscope images of emulsions without (**A**) and with sunscreen agents: $E_{0.5\%Avo}$ (**B**), $E_{2\%Avo}$ (**C**), $E_{0.5\%OMC}$ (**D**), $E_{2\%OMC}$ (**E**).

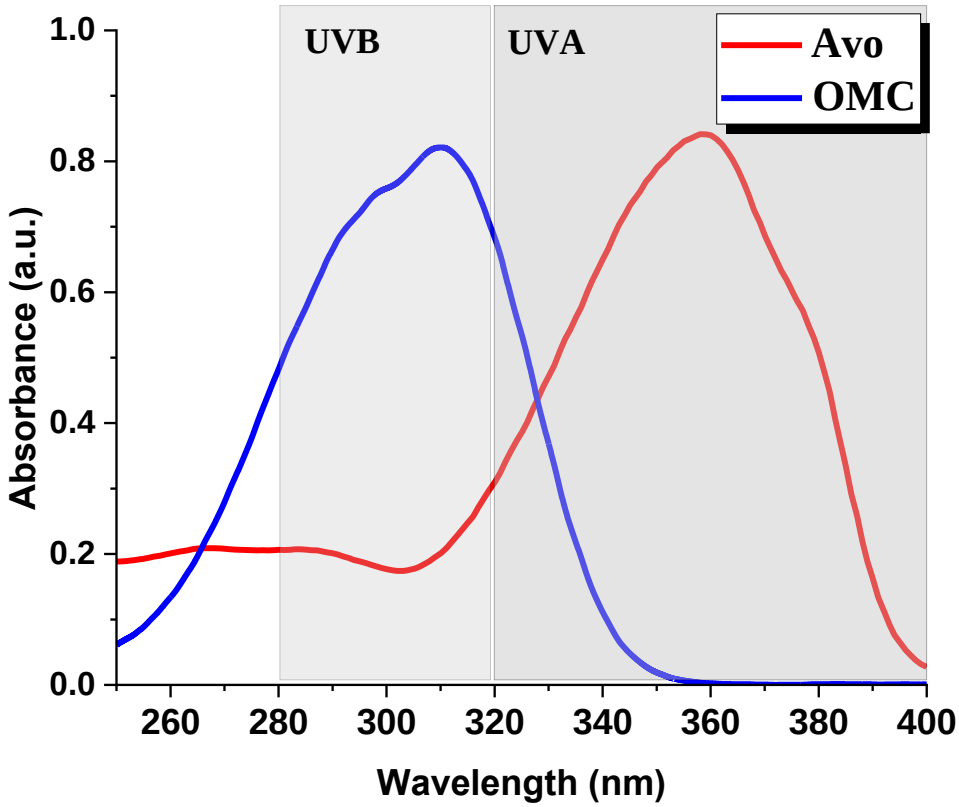


Figure 5. UV spectra of avobenzone and octyl methoxycinnamate in receptor fluid (mixture of ethanol and phosphate buffer of pH 5.8).

The release studies of the UV filters from the emulsions were performed through a cellulose membrane. The results are presented in Figure 6A. The amount of UV filters released after 48 h from the same type of emulsion decreased in the following order $E_{2\%OMC} > E_{0.5\%OMC} > E_{2\%Avo} > E_{0.5\%Avo}$. It was also observed that the diffusion of the UV filters from the formulation to the receptor fluid depended on their concentration. With the increase in Avo/OMC concentration in the emulsion, a higher amount of UV filter was liberated to the receiving medium. It is noteworthy to highlight, that octyl methoxycinnamate diffuses more easily through the cellulose membrane in comparison to avobenzone. These differences in the release profiles may be related to the presence of a lipophilic barrier of oil droplets in the oil-in-water system that retards the release of Avo in the internal oily phase.

Additionally, the solubility of octyl methoxycinnamate is much higher in ethanol (140 mg/mL) than avobenzone (5 mg/L) [52], which could influence the facilitated liberation of the OMC from the formulation to the receptor fluid. Furthermore, different release behaviors between both the UV filters can be associated with their various physicochemical properties. The log P of avobenzone is 4.8, while the calculated log P for OMC is 5.6 [53]. Since octyl methoxycinnamate is more lipophilic than avobenzone (Table 1), different trends in the release rates of both the UV filters can be expected. In other studies, Montenegro et al. prepared six different emulsions with OMC and Avo and observed a much lower amount of avobenzone released through the cellulose membrane compared to octyl methoxycinnamate regardless of the type of formulation used [22]. The avobenzone was not determined in the receptor medium up to 8 h of the experiment. The results confirmed that Avo was liberated from the formulations with intermediate lipophilicity. It implies that the diffusion of the UV filter can be regulated by choosing appropriate ingredients for the topical product. Montenegro et al. also proved that the release patterns of avobenzone and octyl methoxycinnamate were different [54]. It was demonstrated that the emulsifier may influence the permeation of the sunscreen. The release of avobenzone from modified dextrin incorporated into the emulsion was also studied by Li et al. [55]. It was found that the tendency of the UV filter to permeate the skin was significantly reduced due to the modified dextrin compared to the pure emulsion. Another paper presented that Avo was introduced to the oil-in-water emulsion and included in a complex with cyclodextrin. The permeation studies of Avo through rat skin proved that the complexation affects the lag time [56]. In order to understand the mechanism of the UV filter release, the diffusion data were fitted to five different kinetic models (Table 5). The highest correlation coefficient was observed for the Korsmeyer–Peppas model. The n values were higher than 0.45 for all the samples, indicating the anomalous transport. It means that in these cases, in addition to the UV filter diffusion, other mechanisms contribute to the release of OMC and Avo [57].

In the next step, in vitro permeation experiments of the UV filters were performed through a multilayer Strat-M membrane, which is a non-animal-based model recommended for the transdermal analysis, because it mimics human skin [58]. It is composed of a tight top layer coated with a lipid blend similar to that of the human stratum corneum and a porous layer simulating the epidermis and dermis [59]. It was reported that the Strat-M membrane exhibits equivalency to human skin in permeation studies of different compounds [60]. To ensure the solubility of lipophilic sunscreen agents, the receptor compartment was filled with a mixture of ethanol and phosphate buffer with pH 5.8 in the ratio of 1:1. The results of the UV filters permeation studies are presented in Figure 6B. The highest cumulative amount of UV filters released after 48 h was noticed for $E_{2\%OMC}$ followed by $E_{0.5\%OMC}$. In turn, the permeation of avobenzone for both $E_{0.5\%Avo}$ and $E_{2\%Avo}$ was at a very low level after 2 days. The sensitivity of the UV analytical method did not enable to detect avobenzone in the receptor fluid in the first 2 h of analysis. Similar results were obtained by Montenegro and Puglisi [53] who performed the permeation studies of both UV filters through human skin and did not determine avobenzone until 6 h from the beginning of the experiment. It should be highlighted that the action of the active ingredient after topical application occurs in two different steps. Initially, the active compound should diffuse from

the formulation to the skin surface, and after this stage, depending on its physicochemical character, it can permeate the stratum corneum barrier [53]. Based on the results shown in Figure 6B, it can be stated that the rate-limiting step in avobenzone release was not the diffusion from the vehicle but the penetration through the Strat-M membrane, simulating the skin layers. This membrane can act as an additional barrier for lipophilic compounds, such as avobenzone to penetrate. It was calculated that in the case of OMC, around 2% of the UV filter dose was detected in the receptor medium, while for avobenzone ca. 0.2% of the dose permeated through the Strat-M membrane. Very low level of OMC and Avo was also determined by Montenegro et al. [23] who performed permeation studies through human skin. The UV filters were not detected in the receiving phase in the first 8–10 h of measurement. The cumulative amount of Avo, which permeated through the skin was much lower than that of OMC. As it was mentioned above, the difference between the amount of UV filters permeated is attributed to their diverse lipophilicity.

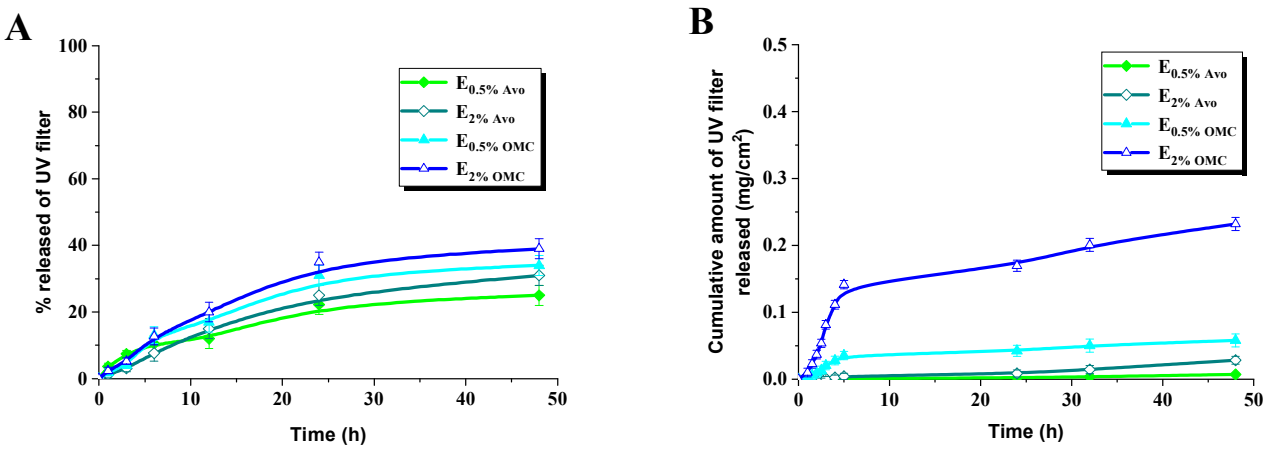


Figure 6. The release profile of avobenzone and octyl methoxycinnamate from emulsions through the cellulose membrane (**A**), and cumulative amount of UV filters permeated through the Strat-M membrane (**B**).

Table 5. Kinetic models used to describe the release of UV filters from oil-in-water emulsions through cellulose membrane.

Sample	Zero Order Model	First Order Model	Higuchi Model	Hixson–Crowell Model	Korsmeyer–Peppas Model	
	Correlation Co-Efficient (R^2)					n
$E_{0.5\%\ Avo}$	0.889	0.898	0.949	0.895	0.964	0.575
$E_{2\%Avo}$	0.968	0.966	0.907	0.961	0.970	0.824
$E_{0.5\%OMC}$	0.880	0.878	0.877	0.879	0.931	0.989
$E_{2\%OMC}$	0.959	0.962	0.931	0.961	0.968	0.978

4. Conclusions

In this report, an efficient preparation procedure for novel oil-in-water emulsions, containing various concentrations of two commonly used chemical filters, avobenzone and octyl methoxycinnamate, was presented. The important aspect was the in vitro permeation experiments through different membranes, which are recently of great interests due to the ban on animal testing for cosmetics. The development of an appropriate methodology to evaluate UV filter penetration will be beneficial for both pharmaceutical and cosmetic industries. The obtained topical formulations did not show phase separation in the centrifuge test performed directly after obtaining and after 35 days of storage at room temperature, regardless of composition. The use of multiple light scattering methods allowed to observe changes in the stability index values. It was established that emulsions with the addition of avobenzone are characterized by the highest stability. The topical formulations show

a pH in the range of 6.02–6.11, which is acceptable for cosmetic products. There were no significant differences in the size of the emulsion particles after the introduction of the selected sunscreen agent.

Due to the growing awareness of the harmful effects caused by UV filters on the skin, release and permeation tests of avobenzone and octyl methoxycinnamate, from the obtained emulsions to receptor fluids at pH 5.8, were carried out. In the assays, cellulose and Strat-M membranes, simulating human skin, were applied. It was found that octyl methoxycinnamate diffuses more easily through the cellulose membrane compared to avobenzone, and the release profiles correspond to the Korsmeyer–Peppas kinetic model. The permeation of the UV filters via the Strat-M membrane occurs to a small extent, which means that they will remain on the skin surface after application. The results obtained support the safety of the formulations containing avobenzone and octyl methoxycinnamate as sunscreen agents providing effective protection against UV radiation. The UV filter lipophilicity mostly affects both the release and permeation through the skin.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/app13137674/s1, Figure S1. Particle size distributions of formulations E, $E_{0.5\%Avo}$, $E_{2\%Avo}$, $E_{0.5\%OMC}$, $E_{2\%OMC}$ after ultrasound treatment; Figure S2. Diagrams of droplet size of formulations E, $E_{0.5\%Avo}$, $E_{2\%Avo}$, $E_{0.5\%OMC}$, $E_{2\%OMC}$.

Author Contributions: Conceptualization, A.O. and J.G.; methodology, A.O.; validation, A.O. and J.G.; investigation, A.O.; data curation, A.O. and J.G.; writing—original draft preparation, A.O.; writing—review and editing, J.G.; visualization, A.O. and J.G.; supervision, J.G.; project administration, A.O.; funding acquisition, A.O. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the National Centre for Research and Development grant number LIDER/5/0036/L-12/20/NCBR/2021.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data available in a publicly accessible repository.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Gasparro, F.P.; Mitchnick, M.; Nash, J.F. A Review of Sunscreen Safety and Efficacy. *Photochem. Photobiol.* **1998**, *68*, 243–256. [CrossRef]
2. Souto, E.B.; Jäger, E.; Jäger, A.; Štěpánek, P.; Cano, A.; Viseras, C.; de Melo Barbosa, R.; Chorilli, M.; Zielińska, A.; Severino, P. Lipid Nanomaterials for Targeted Delivery of Dermocosmetic Ingredients: Advances in Photoprotection and Skin Anti-Aging. *Nanomaterials* **2022**, *12*, 377. [CrossRef] [PubMed]
3. Gholap, A.D.; Sayyad, S.F.; Hatvate, N.T.; Dhumal, V.V.; Pardeshi, S.R.; Chavda, V.P.; Vora, L.K. Drug Delivery Strategies for Avobenzone: A Case Study of Photostabilization. *Pharmaceutics* **2023**, *15*, 1008. [CrossRef] [PubMed]
4. Huang, Z.; Ding, A.; Guo, H.; Lu, G.; Huang, X. Construction of Nontoxic Polymeric UV-Absorber with Great Resistance to UV-Photoaging. *Sci. Rep.* **2016**, *6*, 25508. [CrossRef] [PubMed]
5. Liu, J.; Wang, X.; Zhao, Y.; Xu, Y.; Pan, Y.; Feng, S.; Liu, J.; Huang, X.; Wang, H. Nh3 Plasma Functionalization of UiO-66-NH2 for Highly Enhanced Selective Fluorescence Detection of u (vi) in Water. *Anal. Chem.* **2022**, *94*, 10091–10100. [CrossRef]
6. Egambaram, O.P.; Kesavan Pillai, S.; Ray, S.S. Materials Science Challenges in Skin UV Protection: A Review. *Photochem. Photobiol.* **2020**, *96*, 779–797. [CrossRef]
7. Zhao, Y.-Y.; Wang, X.-B.; Xu, Q.-K.; Chakir, S.; Xu, Y.-F.; Xu, B.; Hu, Y.-H. Micro-/Nanostructured $ZnFe_2O_4$ Hollow Sphere/GO Composite for Structurally Enhanced Photocatalysis Performance. *Rare Metals* **2023**, *42*, 813–821. [CrossRef]
8. Sabzevari, N.; Qiblawi, S.; Norton, S.A.; Fivenson, D. Sunscreens: UV Filters to Protect Us: Part 1: Changing Regulations and Choices for Optimal Sun Protection. *Int. J. Womens Dermatol.* **2021**, *7*, 28–44. [CrossRef]
9. Pantelic, M.N.; Wong, N.; Kwa, M.; Lim, H.W. Ultraviolet Filters in the United States and European Union: A Review of Safety and Implications for the Future of US Sunscreens. *J. Am. Acad. Dermatol.* **2023**, *88*, 632–646. [CrossRef]
10. Klinubol, P.; Asawanonda, P.; Wanichwecharungruang, S.P. Transdermal Penetration of UV Filters. *Skin Pharmacol. Physiol.* **2008**, *21*, 23–29. [CrossRef]

11. Janjua, N.R.; Kongshoj, B.; Andersson, A.; Wulf, H.C. Sunscreens in Human Plasma and Urine after Repeated Whole-body Topical Application. *J. Eur. Acad. Dermatol. Venereol.* **2008**, *22*, 456–461. [CrossRef]
12. Schlumpf, M.; Kypke, K.; Wittassek, M.; Angerer, J.; Mascher, H.; Mascher, D.; Vökt, C.; Birchler, M.; Lichtensteiger, W. Exposure Patterns of UV Filters, Fragrances, Parabens, Phthalates, Organochlor Pesticides, PBDEs, and PCBs in Human Milk: Correlation of UV Filters with Use of Cosmetics. *Chemosphere* **2010**, *81*, 1171–1183. [CrossRef]
13. Kim, S.; Choi, K. Occurrences, Toxicities, and Ecological Risks of Benzophenone-3, a Common Component of Organic Sunscreen Products: A Mini-Review. *Environ. Int.* **2014**, *70*, 143–157. [CrossRef]
14. Gupta, V.K.; Zatz, J.L.; Rerek, M. Percutaneous Absorption of Sunscreens through Micro-Yucatan Pig Skin in Vitro. *Pharm. Res.* **1999**, *16*, 1602–1607. [CrossRef] [PubMed]
15. Arianto, A.; Cella, G.; Bangun, H. Preparation and Evaluation of Sunscreen Nanoemulsions with Synergistic Efficacy on Spf by Combination of Soybean Oil, Avobenzone, and Octyl Methoxycinnamate. *Open Access Maced. J. Med. Sci.* **2019**, *7*, 2751. [CrossRef] [PubMed]
16. Shaath, N. *Sunscreens: Regulations and Commercial Development*; CRC Press: Boca Raton, FL, USA, 2005.
17. Afonso, S.; Horita, K.; e Silva, J.P.S.; Almeida, I.F.; Amaral, M.H.; Lobão, P.A.; Costa, P.C.; Miranda, M.S.; da Silva, J.C.G.E.; Lobo, J.M.S. Photodegradation of Avobenzone: Stabilization Effect of Antioxidants. *J. Photochem. Photobiol. B* **2014**, *140*, 36–40. [CrossRef]
18. Motley, R.J.; Reynolds, A.J. Photocontact Dermatitis Due to Isopropyl and Butyl Methoxy Dibenzoylmethanes (Eusolex 8020 and Parsol 1789). *Contact Dermat.* **1989**, *21*, 109–110. [CrossRef] [PubMed]
19. Cantrell, A.; McGarvey, D.J. Photochemical Studies of 4-Tert-Butyl-4′-Methoxydibenzoylmethane (BM-DBM). *J. Photochem. Photobiol. B* **2001**, *64*, 117–122. [CrossRef]
20. Ambrogi, V.; Latterini, L.; Marmottini, F.; Pagano, C.; Ricci, M. Mesoporous Silicate MCM-41 as a Particulate Carrier for Octyl Methoxycinnamate: Sunscreen Release and Photostability. *J. Pharm. Sci.* **2013**, *102*, 1468–1475. [CrossRef]
21. Ates, G.; Steinmetz, F.P.; Doktorova, T.Y.; Madden, J.C.; Rogiers, V. Linking Existing in Vitro Dermal Absorption Data to Physicochemical Properties: Contribution to the Design of a Weight-of-Evidence Approach for the Safety Evaluation of Cosmetic Ingredients with Low Dermal Bioavailability. *Regul. Toxicol. Pharmacol.* **2016**, *76*, 74–78. [CrossRef]
22. Montenegro, L.; Turnaturi, R.; Parenti, C.; Pasquinucci, L. In Vitro Evaluation of Sunscreen Safety: Effects of the Vehicle and Repeated Applications on Skin Permeation from Topical Formulations. *Pharmaceutics* **2018**, *10*, 27. [CrossRef]
23. Montenegro, L.; Carbone, C.; Paolino, D.; Drago, R.; Stancampiano, A.H.; Puglisi, G. In Vitro Skin Permeation of Sunscreen Agents from O/W Emulsions. *Int. J. Cosmet. Sci.* **2008**, *30*, 57–65. [CrossRef]
24. de Oliveira, C.A.; Peres, D.D.; Graziola, F.; Chacra, N.A.B.; de Araújo, G.L.B.; Florido, A.C.; Mota, J.; Rosado, C.; Velasco, M.V.R.; Rodrigues, L.M. Cutaneous Biocompatible Rutin-Loaded Gelatin-Based Nanoparticles Increase the SPF of the Association of UVA and UVB Filters. *Eur. J. Pharm. Sci.* **2016**, *81*, 1–9. [CrossRef] [PubMed]
25. Shetty, P.K.; Venuvanka, V.; Jagani, H.V.; Chethan, G.H.; Ligade, V.S.; Musmade, P.B.; Nayak, U.Y.; Reddy, M.S.; Kalthur, G.; Udupa, N. Development and Evaluation of Sunscreen Creams Containing Morin-Encapsulated Nanoparticles for Enhanced UV Radiation Protection and Antioxidant Activity. *Int. J. Nanomed.* **2015**, *10*, 6477.
26. Daneluti, A.L.M.; Neto, F.M.; Ruscinc, N.; Lopes, I.; Velasco, M.V.R.; Matos, J.D.R.; Baby, A.R.; Kalia, Y.N. Using Ordered Mesoporous Silica SBA-15 to Limit Cutaneous Penetration and Transdermal Permeation of Organic UV Filters. *Int. J. Pharm.* **2019**, *570*, 118633. [CrossRef] [PubMed]
27. Lin, Y.-C.; Lin, C.-F.; Alalaiwe, A.; Wang, P.-W.; Fang, Y.-P.; Fang, J.-Y. UV Filter Entrapment in Mesoporous Silica Hydrogel for Skin Protection against UVA with Minimization of Percutaneous Absorption. *Eur. J. Pharm. Sci.* **2018**, *122*, 185–194. [CrossRef] [PubMed]
28. Blasi, P.; Schoubben, A.; Giovagnoli, S.; Rossi, C.; Ricci, M. The Real Value of Novel Particulate Carriers for Sunscreen Formulation. *Expert Rev. Dermatol.* **2011**, *6*, 509–517. [CrossRef]
29. Palm, M.D.; O'Donoghue, M.N. Update on Photoprotection. *Dermatol. Ther.* **2007**, *20*, 360–376. [CrossRef]
30. Jiménez, M.M.; Pelletier, J.; Bobin, M.F.; Martini, M.C. Influence of Encapsulation on the in Vitro Percutaneous Absorption of Octyl Methoxycinnamate. *Int. J. Pharm.* **2004**, *272*, 45–55. [CrossRef]
31. Yener, G.; Incegül, T.; Yener, N. Importance of Using Solid Lipid Microspheres as Carriers for UV Filters on the Example Octyl Methoxy Cinnamate. *Int. J. Pharm.* **2003**, *258*, 203–207. [CrossRef]
32. Scalia, S.; Tursilli, R.; Bianchi, A.; Nostro, P.L.; Bocci, E.; Ridi, F.; Baglioni, P. Incorporation of the Sunscreen Agent, Octyl Methoxycinnamate in a Cellulosic Fabric Grafted with β-Cyclodextrin. *Int. J. Pharm.* **2006**, *308*, 155–159. [CrossRef] [PubMed]
33. Andreani, T.; Dias-Ferreira, J.; Fangueiro, J.F.; Souza, A.L.R.; Kiill, C.P.; Gremião, M.P.D.; García, M.L.; Silva, A.M.; Souto, E.B. Formulating Octyl Methoxycinnamate in Hybrid Lipid-Silica Nanoparticles: An Innovative Approach for UV Skin Protection. *Heliyon* **2020**, *6*, e03831. [CrossRef]
34. Goscianska, J.; Olejnik, A.; Nowak, I.; Marciniak, M.; Pietrzak, R. Ordered Mesoporous Silica Modified with Lanthanum for Ibuprofen Loading and Release Behaviour. *Eur. J. Pharm. Biopharm.* **2015**, *94*, 550–558. [CrossRef] [PubMed]
35. Filippa, L.; Trento, A.; Álvarez, A.M. Sauter Mean Diameter Determination for the Fine Fraction of Suspended Sediments Using a LISST-25X Diffractometer. *Measurement* **2012**, *45*, 364–368. [CrossRef]
36. Olejnik, A.; Panek, R.; Madej, J.; Franus, W.; Goscianska, J. Low-Cost Zeolitic Carriers for Delivery of Hydroxychloroquine Immunomodulatory Agent with Antiviral Activity. *Micropor. Mesopor. Mater.* **2022**, *346*, 112315. [CrossRef]

37. Smaoui, S.; Hlima, H.B.; Chobba, I.B.; Kadri, A. Development and Stability Studies of Sunscreen Cream Formulations Containing Three Photo-Protective Filters. *Arab. J. Chem.* **2017**, *10*, S1216–S1222. [CrossRef]
38. Schmid-Wendtner, M.-H.; Korting, H.C. The PH of the Skin Surface and Its Impact on the Barrier Function. *Skin Pharmacol. Physiol.* **2006**, *19*, 296–302. [CrossRef]
39. Available online: https://nyscc.org/blog/sunscreen-formulations-emphasis-on-inorganic-sunscreens/ (accessed on 19 May 2023).
40. Das, P.; Das, M.K. Production and Physicochemical Characterization of Nanocosmeceuticals. In *Nanocosmeceuticals*; Elsevier: Amsterdam, The Netherlands, 2022; pp. 95–138.
41. Olejnik, A.; Kapuscinska, A.; Schroeder, G.; Nowak, I. Physico-Chemical Characterization of Formulations Containing Endomorphin-2 Derivatives. *Amino Acids* **2017**, *49*, 1719–1731. [CrossRef]
42. Trujillo-Cayado, L.A.; Ramírez, P.; Alfaro, M.C.; Ruíz, M.; Muñoz, J. Adsorption at the Biocompatible α-Pinene–Water Interface and Emulsifying Properties of Two Eco-Friendly Surfactants. *Colloids Surf. B Biointerfaces* **2014**, *122*, 623–629. [CrossRef]
43. Celia, C.; Trapasso, E.; Cosco, D.; Paolino, D.; Fresta, M. Turbiscan Lab® Expert Analysis of the Stability of Ethosomes® and Ultradeformable Liposomes Containing a Bilayer Fluidizing Agent. *Colloids Surf. B Biointerfaces* **2009**, *72*, 155–160. [CrossRef]
44. Mengual, O.; Meunier, G.; Cayré, I.; Puech, K.; Snabre, P. TURBISCAN MA 2000: Multiple Light Scattering Measurement for Concentrated Emulsion and Suspension Instability Analysis. *Talanta* **1999**, *50*, 445–456. [CrossRef] [PubMed]
45. Carbone, C.; Musumeci, T.; Lauro, M.R.; Puglisi, G. Eco-Friendly Aqueous Core Surface-Modified Nanocapsules. *Colloids Surf. B Biointerfaces* **2015**, *125*, 190–196. [CrossRef] [PubMed]
46. Liu, S.; Tan, G. Lubricating Properties of Oil-in-Water Emulsion with Low Oil Concentration: Competitive Wetting Effect. *Sci. China Technol. Sci.* **2013**, *56*, 369–375. [CrossRef]
47. Hashim, A.A.-J.; Rajab, N.A.; Tekie, F.S.M.; Dinarvand, R.; Akrami, M. Investigations Factors Affecting Formulation of Anastrozole as Nanostructured Lipid Carrier. *Int. J. Pharm. Res.* **2020**, *12*, 937–945.
48. André, V.; Willenbacher, N.; Debus, H.; Börger, L.; Fernandez, P.; Frechen, T.; Rieger, J. Prediction of Emulsion Stability: Facts and Myth. *Cosmet. Toilet. Manuf. Worldw.* **2003**, *102*, 220–231.
49. Wester, R.C.; Maibach, H.I. Cutaneous Pharmacokinetics: 10 Steps to Percutaneous Absorption. *Drug Metab. Rev.* **1983**, *14*, 169–205. [CrossRef]
50. Németh, Z.; Pirger, Z.; Fodor, I.; Óvári, M.; Komáromy, A. Analytical Methods for Investigating the Presence, Photoisomerisation-, and Degradation Kinetics of the UV-A Filter Avobenzone under Aqueous Conditions to Ensure a More Realistic Environmental Measurement. *J. Photochem. Photobiol. A Chem.* **2023**, *439*, 114621. [CrossRef]
51. Miranda, M.S.; Pinto da Silva, L.; Esteves da Silva, J.C.G. UV Filter 2-ethylhexyl 4-methoxycinnamate: A Structure, Energetic and UV–Vis Spectral Analysis Based on Density Functional Theory. *J. Phys. Org. Chem.* **2014**, *27*, 47–56. [CrossRef]
52. Available online: https://cdn.caymanchem.com/cdn/insert/23836.pdf (accessed on 25 May 2023).
53. Montenegro, L.; Puglisi, G. Evaluation of Sunscreen Safety by In Vitro Skin Permeation Studies: Effects of Vehicle Composition. *Die Pharm. Int. J. Pharm. Sci.* **2013**, *68*, 34–40.
54. Montenegro, L.; Paolino, D.; Puglisi, G. Effects of Silicone Emulsifiers on In Vitro Skin Permeation of Sunscreens from Cosmetic Emulsions. *J. Cosmet. Sci.* **2004**, *55*, 509–518.
55. Li, C.-C.; Lin, L.-H.; Lee, H.-T.; Tsai, J.-R. Avobenzone Encapsulated in Modified Dextrin for Improved UV Protection and Reduced Skin Penetration. *Chem. Pap.* **2016**, *70*, 840–847. [CrossRef]
56. Tampucci, S.; Burgalassi, S.; Chetoni, P.; Monti, D. Cutaneous Permeation and Penetration of Sunscreens: Formulation Strategies and in Vitro Methods. *Cosmetics* **2017**, *5*, 1. [CrossRef]
57. Fosca, M.; Rau, J.V.; Uskoković, V. Factors Influencing the Drug Release from Calcium Phosphate Cements. *Bioact. Mater.* **2022**, *7*, 341–363. [CrossRef] [PubMed]
58. Arce, F.J.; Asano, N.; See, G.L.; Itakura, S.; Todo, H.; Sugibayashi, K. Usefulness of Artificial Membrane, Strat-M®, in the Assessment of Drug Permeation from Complex Vehicles in Finite Dose Conditions. *Pharmaceutics* **2020**, *12*, 173. [CrossRef]
59. Haq, A.; Goodyear, B.; Ameen, D.; Joshi, V.; Michniak-Kohn, B. Strat-M® Synthetic Membrane: Permeability Comparison to Human Cadaver Skin. *Int. J. Pharm.* **2018**, *547*, 432–437. [CrossRef] [PubMed]
60. Uchida, T.; Kadhum, W.R.; Kanai, S.; Todo, H.; Oshizaka, T.; Sugibayashi, K. Prediction of Skin Permeation by Chemical Compounds Using the Artificial Membrane, Strat-M™. *Eur. J. Pharm. Sci.* **2015**, *67*, 113–118. [CrossRef] [PubMed]