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Article

Addition of Trans-Resveratrol-Loaded, Highly Concentrated Double Emulsion to Moisturizing Cream: Effect on Physicochemical Properties

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Abstract: Resveratrol is a compound increasingly studied for its many beneficial properties for health. However, it is a highly unstable photosensitive compound, and therefore it is necessary to encapsulate it to protect it if you want to use it in a commercial product. Emulsions are systems that allow the encapsulation of active ingredients, protecting them and allowing their release in a controlled manner. They are highly used systems in the pharmaceutical, cosmetic and food industries. The main objectives of this work are to study the feasibility of encapsulating resveratrol in concentrated water-in-oil-in-water double emulsions and the effect produced by adding the double emulsion with optimal formulation to a commercial cream for cosmetic applications. The effect of the selected optimal double emulsion on a commercial cream was studied, analyzing droplet size distribution, morphology, stability and rheology. The main conclusion of this work is that incorporating 1/3 of concentrated double emulsion $W_1/O/W_2$ into a commercial moisturizing cream had a positive physical effect and produced cream with a resveratrol concentration of up to 0.0042 mg/g.

Keywords: trans-resveratrol; encapsulation; high internal phase double emulsions; moisturizing cream

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1. Introduction

Resveratrol (3,5,4′-trihydroxy-trans-stilbene), or RSV, is a polyphenol of the stilbene family that, due to its antioxidant character, seems to produce beneficial effects on human health, which has greatly increased its applications in different types of industries such as pharmaceuticals or cosmetics [1,2]. Several therapeutic properties of resveratrol are currently being studied, such as its ability to prevent cardiovascular or neurodegenerative diseases [3–5]. Although probably the most striking are its anticancer properties, hindering the spread of cancer as well as its initiation [6–10], being especially effective against possible skin cancer [11]. However, the property that has aroused the interest of the cosmetic industry in this compound is its antiaging effect, a consequence of its antioxidant properties [12,13]. According to previous studies, one of the properties of resveratrol is that it helps to retard skin aging since it helps protect cellular DNA from free radicals [14]. That is why the cosmetic industry is interested in the incorporation of resveratrol into creams or gels.

However, regarding resveratrol's physicochemical properties, it has a low solubility in water (0.03 g/L) compared to its high solubility in ethanol (50 g/L) [15], and its great UV, pH or thermal instability [15–21] are especially noteworthy.

Due to its low stability, it is necessary to protect it in order to slow down or even prevent its loss while increasing its bioavailability [22]. This can be achieved by encapsulating it with one of the currently available methods. One of the most prominent is using emulsions.

An emulsion is a heterogeneous liquid system of at least two phases in which one called the dispersed or internal phase is dispersed in the form of drops into another called the continuous or external phase. The liquid phases that compose the emulsions (typically water and oil) are immiscible with each other, making them highly unstable systems. To prevent droplet coalescence, stabilizing agents (surfactants, particles or proteins) are added at the interface.

The main two types of emulsions are oil-in-water (O/W) and water-in-oil (W/O). These types of systems possess the capacity to encapsulate antioxidant compounds of other bioactive compounds in their inner phase, which can be transported to desired points. Moreover, more complex emulsions systems can be found, as in the case of double emulsions, which are ternary systems where the dispersed droplets contain smaller droplets. Two main types to distinguish are water-in-oil-in-water ($W_1/O/W_2$) or oil-in-water-in-oil ($O_1/W/O_2$).

Emulsions are widely used to encapsulate compounds of interest for several bioapplications, such as polyphenols, lutein or vitamins [23–30]. Emulsions protect active compounds to maintain their desired properties and offer a controlled release of the encapsulated compounds. Emulsions are widely used in the cosmetic industry, and they are a good mechanism for encapsulating different active ingredients since they are found in the dispersed phase and the continuous phase would act as a barrier to protect them from the outside environment, thus increasing their stability and consequently their useful life. They also allow a controlled release. Double emulsions allow the encapsulating of aqueous soluble compounds in an aqueous matrix. Moreover, the organic intermediate phase offers an additional barrier for biocompound release, which enhances encapsulation and controlled release.

Incorporating active ingredients in cosmetic products was widely performed in the 1990s, and as a consequence, the term 'cosmeceutical' appeared, combining the terms 'cosmetic' and 'pharmaceutical' [31]. While a conventional cosmetic product is intended for beauty, a cosmeceutical product is intended to influence the biological functions of the skin by incorporating active ingredients. It is important in cosmeceutical products, as in the case of pharmaceuticals, that the encapsulated active ingredient should have a concentration above a certain threshold concentration, which is different for each compound, hence the importance of achieving highly concentrated double emulsions to arise a large biocompound concentration in the final product.

For this reason, the feasibility of encapsulating resveratrol in concentrated water in oil-in-water double emulsions formulated with Polyglycerol polyricinoleate (PGPR) and Tween 20 stabilizers has been studied. Moreover, the effect produced by the addition of the double emulsion to a commercial cream for cosmetic applications in order to take advantage of the benefits of the biocompound through its dermal application has been investigated.

2. Materials and Methods

2.1. Materials

Absolute ethanol, RSV, and Tween® 20 (polyoxyethylenesorbitan monolaurate) were purchased from Sigma Aldrich (San Louis, MO, USA). Miglyol® 812 (density 945 kg/m^3 at 20 °C), which is a neutral oil formed by esters of caprylic and capric fatty acids and glycerol, was supplied by Sasol GmbH (Hambuerg, Germany). Polyglycerol polyricinoleate (PGPR) was obtained from Brenntag AG (Frankfurt, Germany). Sodium chloride was supplied by Panreac (Barcelona, Spain), and the moisturizing cream was a balancing cream for normal-oily skin from the Deliplus brand acquired from the Mercadona supermarket chain.

2.2. Methods

2.2.1. Water-in-Oil (W_1/O) Inner Emulsion Preparation

The internal emulsion (W_1/O) was prepared with 30 vol.% of internal aqueous phase (W_1) and 70 vol.% of oily phase (O). As oily phase, Miglyol 812 containing 5 wt.% of the hydrophobic emulsifier (PGPR) was used. PGPR was previously dissolved in the oily phase by magnetic stirring at room temperature for 30 min. PGPR was selected since it is a common stabilizer in food formulations with highly stabilizing effect [32–34].

RSV has low water solubility, and its solubility in alcohol decreases as the carbon number of the alcohol increases [35]. For this reason, 20% ethanol (*v*/*v*) was used in the W_1. Moreover, a concentration of 50 mg/L of RSV was incorporated into the W_1 solution.

Additionally, 0.1M NaCl was added to W_1 to ensure aqueous droplet stability since it has been found that the addition of electrolytes to aqueous phases increases emulsion stability [32,36,37].

Both phases were placed together in glass vessels and emulsified by high-shear mixing at 15,000 rpm for 5 min using Silentcruser M Homogenizer (Heidolph, Germany) with a 6 mm dispersing tool.

2.2.2. Water-in-Oil-in-Water (W_1/O/W_2) Double Emulsions Preparation

W_2 was composed of a 2% (*w*/*v*) Tween 20 solution, which was ensured to have more than 300 times the CMC value [38,39]. In order to equilibrate the osmotic pressure of both aqueous phases, 0.1M NaCl was also added to the W_2 [40].

The W_1/O/W_2 double emulsions were formulated, dispersing the W_1/O primary emulsion, and incorporated into W_2 at the volumetric ratios of W_1/O in W_2: 80/20.

This second emulsification step was carried out by mixing the inner emulsion and external aqueous phase at 5000 rpm for 2 min with the aforementioned Silentcruser M Homogenizer. Milder agitation conditions were used in order to avoid the rupture of the inner emulsion W_1/O, producing a final simple O/W emulsion.

Emulsification conditions and emulsion formulation parameters were selected according to the optimal results obtained in previous studies [24,41,42].

2.2.3. Addition of Trans-Resveratrol-Loaded, Highly Concentrated Double Emulsion (W_1/O/W_2) to Moisturizing Cream

Once the optimal formulation for the double emulsions had been chosen by considering the results of previous studies [42], its effect was studied by mixing it with a commercial cream with proportions of 1/4, 1/3 and 1/2 emulsion (*w*/*w*). The mixture between the cream and the emulsion was carried out by manual agitation.

2.2.4. Characterization

The influence of incorporating a double emulsion in its optimal formulation to a commercial cream was studied.

The same parameters were studied for a commercial cream as well as for a mixture between the commercial cream and the incorporation of the double emulsion in proportions of 1/4, 1/3 and 1/2 emulsion.

The double emulsions were previously characterized in terms of droplet size distribution, stability, encapsulation efficiency and rheology [42].

Droplet Size Distribution and Morphology

The droplet size distribution was measured with the long-bench Mastersizer S (Malvern Instruments Ltd., Malvern, UK) based on diffraction of laser radiation. A representation of the different sizes and volume occupied by them was obtained. The size results were expressed in equivalent sphere diameter, that is, the diameter of the sphere that has the same volume as the measured particle. Although for emulsions, spherical droplets can be assumed. The refractive index of the Miglyol 812 (1.54) was used for double emulsions droplet size measurements.

Micrographs of the emulsions were obtained with an Olympus BX50 light microscope (Olympus, Tokyo, Japan) with 10–100× magnification using UV–vis and fluorescence lamps. Micrographs were used for visual inspection of emulsions and to confirm the droplet size obtained by laser light scattering.

Colloidal Stability

Dispersed phase droplets could produce emulsion destabilization due to the migration of the low-density drops to the top part of the container, producing a top layer rich in droplets and a top layer formed mainly by external continuous phase. This destabilization phenomenon is known as creaming.

The stability of the moisturizing cream and its mixture with double emulsions was determined with the TurbiscanLabExpert (Formulaction, Toulouse, France). This instrument emits a light beam that passes through the sample and measures transmission and backscattering of the light beam.

Samples without dilution were placed in the cells. Transmitted and backscattered light was monitored as a function of time and cell height. The optical reading head scans the sample in the cell, providing TS and BS data every 40 μm as a function of the sample height (in mm). The obtained profiles built up a macroscopic fingerprint of the cream or mixture, providing useful information about sample changes with time [27].

Rheology

The rheological tests were carried out with a Haake MARS II rotational rheometer with a Haake UTC Peltier temperature control unit. All the analyses were developed at 25 ± 0.1 °C, employing a parallel-plate sensor system (PP60Ti) with a gap of 1 mm. Before starting any measurement, the sample rested for at least 5 min, allowing the stresses induced during sample load to relax.

Viscosity measurements were conducted in control rate (CR) mode from 0 to 1000 s^{-1} for 300 s. Herschel–Bulkley model, commonly used to characterize different hydrocolloid dispersions and food emulsions [43], has been selected to fit the flow curves obtained

$$\tau = \tau_0 + K\dot{\gamma}^n \quad (1)$$

where τ is the shear stress (Pa), τ_0 is the yield point (Pa), $\dot{\gamma}$ is the shear rate (s^{-1}), K is the consistency coefficient (Pa s^n) and n is the flow behavior index (-).

The frequency sweeps were carried out from 10 to 0.1 Hz at a constant shear stress of 0.1 Pa.

All measurements were developed at least in triplicate.

Texturometry

Texturometry measurements were performed with a TA.XT.plus Texture Analyzer (Stable Micro Systems, Godalming, UK). A load cell of 5000 g was used as a penetration test, a 5 mm penetration was made with a 0.5 in. diameter probe (S/0.5) at a speed of 2 mm/s. Force versus time was recorded. Maximum force was taken as a measurement of hardness, while the maximum negative force was taken as an indication of stickiness. Test was made at room temperature and measurements were developed in duplicate.

3. Results and Discussion

In light of the results of the previous studies [42], the optimal formulation chosen was the double emulsion $W_1/O/W_2$ with a proportion of 80/20 with an internal phase W_1/O with a proportion of 30/70. How the addition of this emulsion to a commercial cream affected the physicochemical properties was studied.

3.1. Droplet Size Distribution and Morphology

Figure 1 shows the results of the droplet size distribution for the double emulsion and commercial cream as well as the mixtures of the commercial cream and optimal formulation chosen in proportions of 1/2, 1/3 and 1/4 emulsion.

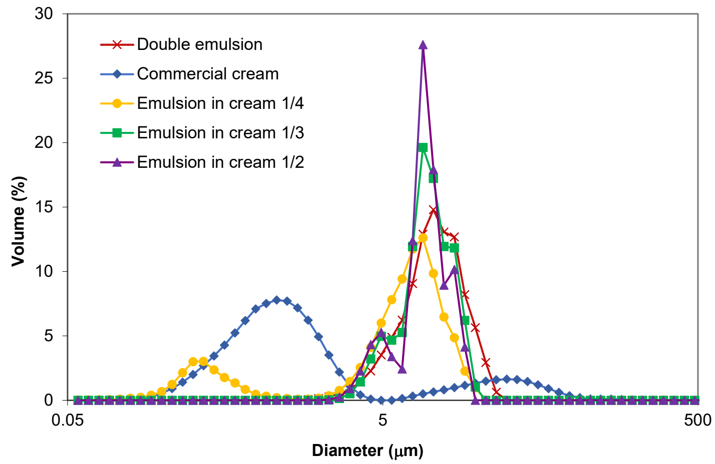

Figure 1. Droplet size distribution of double emulsion, commercial cream and cream-emulsion mixtures.

The results of Figure 1 show that mixing the emulsion has a great influence on the droplet size, considerably displacing the main peak to the right and producing an increase in the average droplet size. It can be observed that the main peaks of the mixtures are similar to the main peak obtained for the double emulsion droplet size distribution.

It can also be seen how, as a greater amount of emulsion is incorporated, the size distribution of the commercial cream (the peak at low sizes) is transformed into the typical size distribution of double emulsions with an internal emulsion ratio of 30/70 [42,44]. Thus, it can be observed how the mixture that contains the lowest proportion of emulsion shows its first peak close to the main peak of the size distribution of the cream, and a second typical peak of the double emulsions of the same internal concentration appears. As the amount of emulsion in the mixture increased, the size distribution obtained became similar to that of the double emulsion itself [44].

A similar trend was observed in previous studies when the emulsion was incorporated into yogurt. It was seen that in all samples, the presence of emulsion affects the size distribution of the matrix [45]. In the present case, the addition of the emulsion caused an increase in the average droplet size and produced a bimodal distribution as was observed in the case when the emulsion was incorporated into the food matrix [45]. Moreover, the addition of RSV has been found to have some interactions with the matrix where it is incorporated since its presence produces physical changes in the system [46].

It is also important to point out that mixed systems with 1/3 and 1/2 of emulsion on cream present a narrower size distribution than double emulsion itself, which is more noticeable as the emulsion ratio in cream increases. It can be also observed that the presence of the smaller droplets (around 5 μm) disappears when the emulsion portion on the cream increases. This behavior indicates a clear interaction of both systems.

The microscope images obtained for the different samples are shown below in Figure 2.

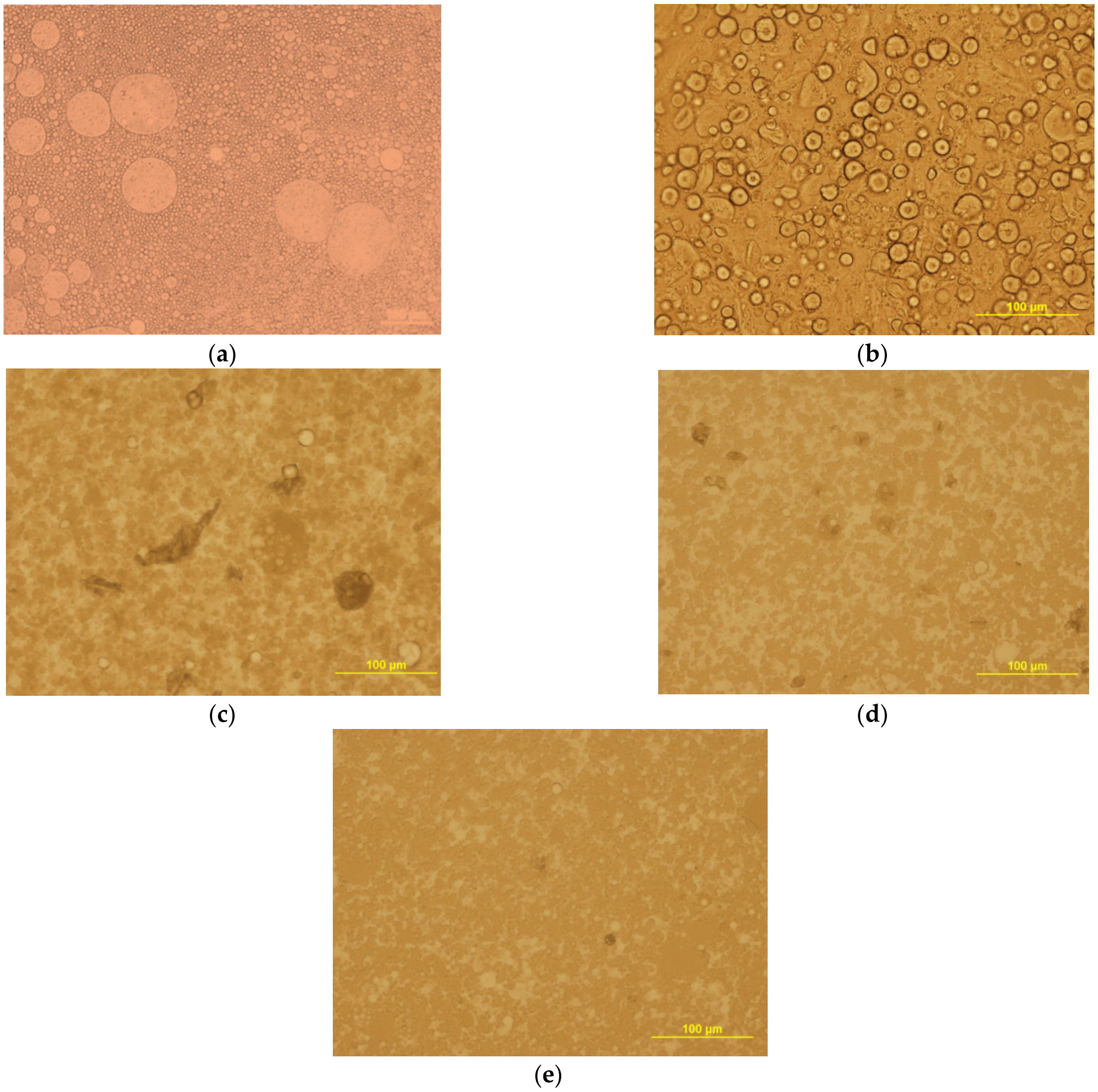

Figure 2. Micrographs of the commercial cream and mixtures of the commercial cream with the double emulsion $W_1/O/W_2$ of concentration 80/20 with an internal phase ratio W_1/O of 30/70: (**a**) double emulsion; (**b**) commercial cream; (**c**) commercial cream with 1/4 emulsion; (**d**) commercial cream with 1/3 emulsion and (**e**) commercial cream with 1/2 emulsion.

It can be observed the individual and large particle sizes registered on the double emulsion (Figure 2a). Moreover, it can be seen how the commercial cream is highly structured but with a lower droplet size (Figure 2b). It is difficult to quantify and compare the concentration of dispersed phases in both individual systems. However, it can be noticed that double emulsion seems to have a larger internal fraction than the commercial cream, which could be because of the large droplet size measured when the mixtures are characterized.

In the mixtures, it can be observed that the structure observed in the commercial cream is broken, even with just a quarter (Figure 2c), and it is even more noticeable when a larger proportion of emulsion is added. This confirms the interaction observed in Figure 1 between both systems, in which clear interaction of both systems is observed in the mixtures. It is difficult to appreciate individual large drops in the mixed systems as in the cases of plain emulsion or plain cream which could indicate that the measurements made by the laser diffraction technique could be responsible for the measurements of agglomerates produced by the interaction of emulsion droplets that could be acting as flocculants of individual cream droplets.

3.2. Colloidal Stability

The results of the stability measurements are shown in Figure 3.

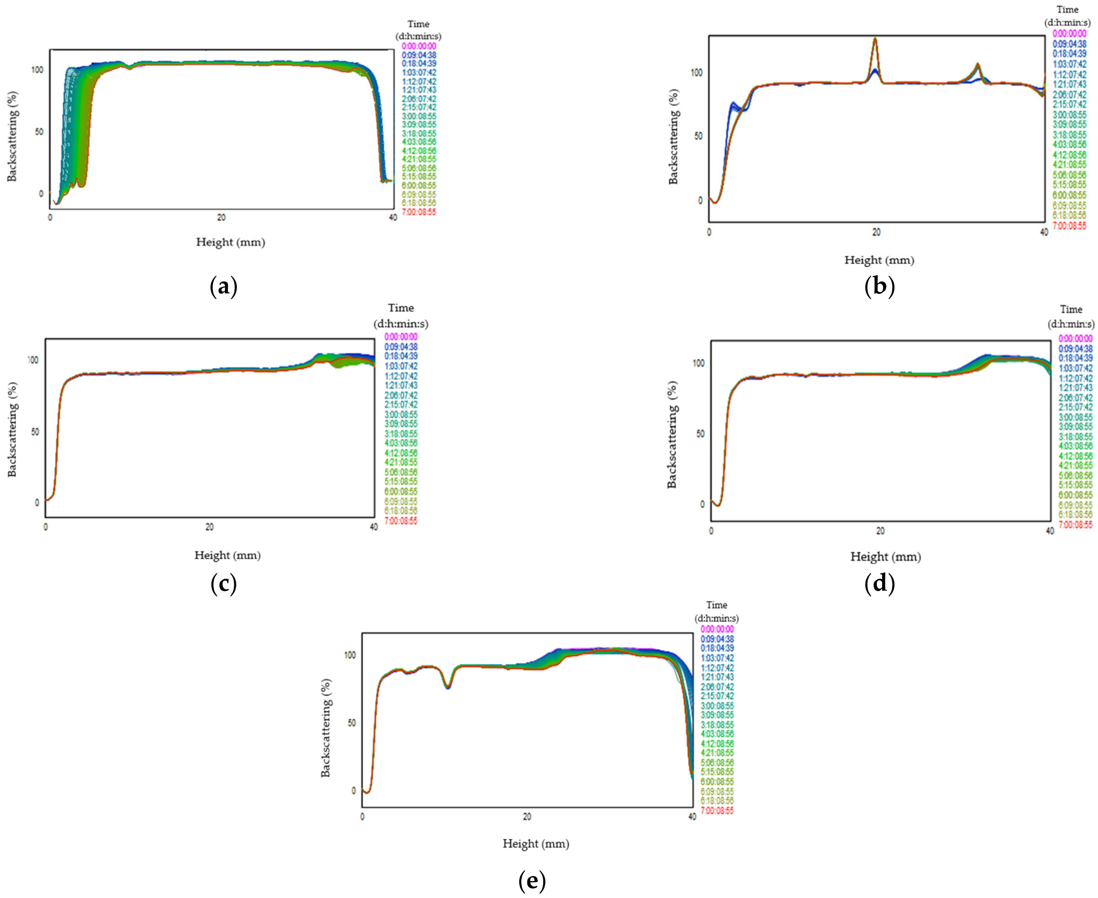

Figure 3. Measurements of the stability of the commercial cream and mixtures of the commercial cream with the double emulsion $W_1/O/W_2$ of concentration 80/20 with an internal phase ratio W_1/O of 30/70: (**a**) double emulsion; (**b**) commercial cream; (**c**) commercial cream with 1/4 emulsion; (**d**) commercial cream with 1/3 emulsion and (**e**) commercial cream with 1/2 emulsion.

It can be observed that double emulsion presents a clarification on the bottom part of the cell (Figure 3a), which is not appreciable when this emulsion was mixed with the commercial cream. This is probably due to the large viscosity of the sample, which increases the stability of the system versus clarification or creaming phenomena.

On the other hand, plain commercial cream presented high stability (Figure 3b). However, when adding the emulsion, it can be seen how the backscattering decreases slightly, especially in the upper part of the cell. Particularly in the case when 1/2 of emulsion was included in the commercial cream, a change on the top part of the system was observed, indicating an instability process related to creaming, probably due to drop coalescence, which seems to be promoted by the interaction between both systems. This creaming effect is less noticeable when 1/4 and 1/3 of emulsion were added to the commercial cream.

3.3. Rheology

Viscosity measurements are shown in Figure 4. It can be observed that the commercial cream presents a typical pseudoplastic behavior, while the behavior registered for the double emulsion is closer to a Newtonian fluid [47]. In the case of the mixtures, it can be observed that all of them present a pseudoplastic character. The case when 1/2 of emulsion was added to the mixture is less pronounced, which indicates a high influence of the emulsion on the system viscosity.

It is also important to consider that commercial cream viscosity is up to 10^5 times higher than that showed by the emulsion at low shear rates (value around 0.0015 s^{-1}), arising intermediate values for the mixed systems. However, these differences became lower as shear rate increased, showing close values for the commercial cream and mixtures at shear rates of 500 s^{-1}, the point at which the viscosity of the emulsion is 10 times lower than the viscosity of the samples that contain commercial cream.

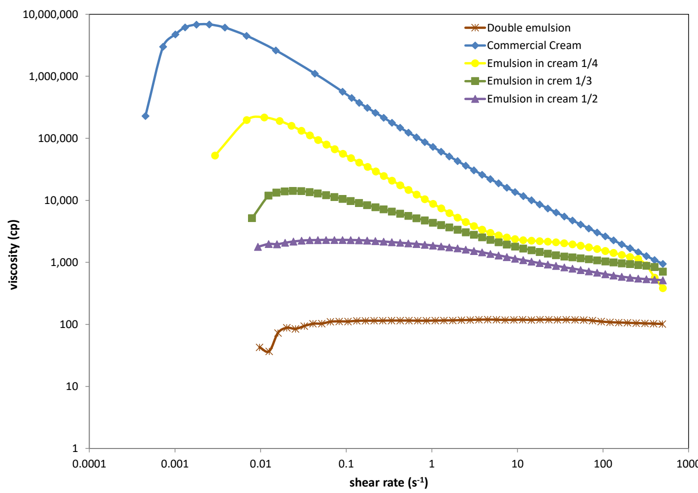

Figure 4. Viscosity measurements of the commercial cream and mixtures of the commercial cream with the double emulsion $W_1/O/W_2$ of concentration 80/20 with an internal phase ratio W_1/O of 30/70.

The parameter values obtained from the Herschel–Bulkley model fitting to the flow curve data for all the samples are shown in Table 1.

Table 1. Parameter values obtained fitting the Herschel–Bulkley rheological model to flow curve data of measured samples.

Sample	Herschel–Bulkley		
	τ_0	k	n
Double emulsion	0.020 ± 0.002	0.149 ± 0.003	0.940 ± 0.003
Commercial cream	18.860 ± 2.202	47.220 ± 5.128	0.356 ± 0.019
Mixture ¼	28.940 ± 5.165	51.070 ± 6.304	0.344 ± 0.047
Mixture 1/3	5.643 ± 0.412	46.000 ± 5.402	0.220 ± 0.052
Mixture ½	−3.103 ± 0.107	5.985 ± 0.602	0.710 ± 0.171

When considering the Herschel–Bulkley model, a relatively high value of the yield point, the stress at which a material begins to deform plastically, is observed in the commercial cream [48], whereas for the double emulsion, the value is close to zero. The yield point increases when mixing a quarter of emulsion but notably decreases in the other mixtures. The n-value indicates the almost Newtonian character (n = 0.94) observed for the double emulsion. The n-value is lower in the case of the mixture of commercial cream and

½ of double emulsion up to a value of 0.71. However, the commercial cream presented an *n*-value of 0.36, close to that registered for the mixtures with 1/4 of double emulsion, which indicates the presence of ¼ of emulsion does not affect the flow behavior of the sample.

In Figure 5, results obtained from the frequency sweep analysis are shown. The elastic (G′) and the viscous (G″) moduli are represented vs. the frequency. These tests provide information about the viscoelastic character of the samples.

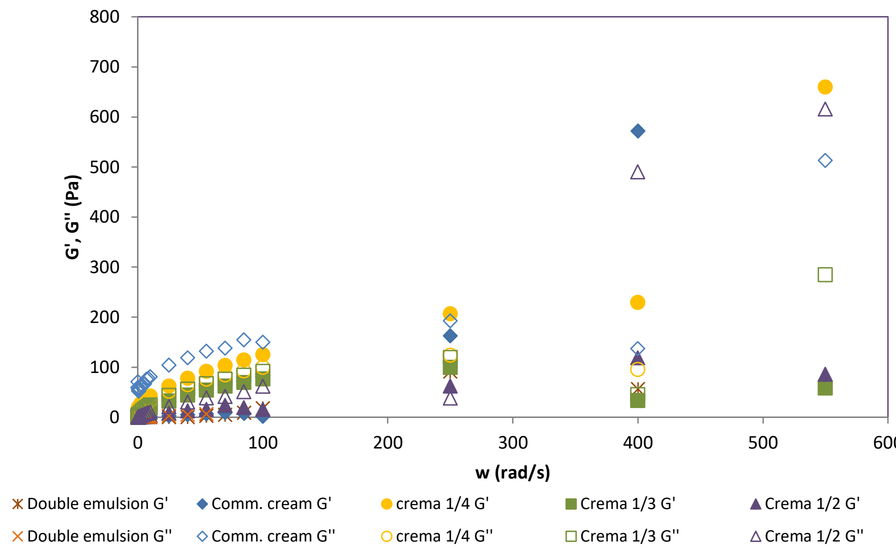

Figure 5. Frequency sweeps of the commercial cream and mixtures of the double emulsion, commercial cream and mixtures cream and double emulsion.

It can be seen that the double emulsion presents a larger G″ than G′, which indicates a character more viscous than elastic. On the contrary, the commercial cream shows a behavior notably more elastic than viscous (G′ > G″) in all the frequency ranges studied.

Observing the mixtures, it can be appreciated that when just 1/4 of emulsion is added to the cream, the samples still have a larger elastic modulus than viscous. However, when 1/3 of the emulsion is added, the values of both moduli were closer, except for the high frequency (550 rad/s) point at which G″ > G′. This fact is even more pronounced when 1/2 of emulsion is added, showing a behavior similar to that exhibited by the double emulsion.

3.4. Texturometry

Texturometry results are shown in Table 2.

Table 2. Results of the texturometry tests for the commercial cream and mixtures of the commercial cream with the double emulsion $W_1/O/W_2$ of concentration 80/20 with an internal phase ratio W_1/O of 30/70.

Sample	Hardness (N)	Stickiness (N)
Commercial cream	0.182 ± 0.002	−0.140 ± 0.002
Mixture ¼	0.212 ± 0.004	−0.160 ± 0.004
Mixture 1/3	0.268 ± 0.004	−0.175 ± 0.006
Mixture ½	0.056 ± 0.001	−0.037 ± 0.002

According to hardness values, it can be seen that the addition of the emulsion barely affects the firmness of the commercial sample until a high proportion of emulsion is achieved, i.e., the mixture ½ showed a notably lower value of hardness in comparison with the rest of the samples. A similar trend is observed regarding stickiness (which has a negative value simply because it is a force exerted in the opposite direction) since the ½ sample exhibited the lowest stickiness value. Again, this is due to the fact that this sample has a higher proportion of emulsion.

According to the literature, hardness differences below 13% are not perceptible by touch. Moreover, the change in the perception of stickiness seems to be insignificant when the differences are below 6–8% [49–51]. The registered values indicate that even the addition of 1/4 of emulsion to the mixture has acceptable changes in hardness, whereas the presence of double emulsion could produce noticeable changes in stickiness in comparison to cream. However, it is important to point out the wide range of creams and cosmetics that are commercially available, which entails a wide range of different textural properties [51,52].

4. Conclusions

The presence of emulsion in commercial cream considerably changed the values of the parameters studied. However, its appearance is still acceptable. By increasing the amount of emulsion in the mixture above a third of the total, the cream structure suffered breakage and partial destabilization of the mixture.

The predominant droplet size increased considerably when adding emulsion to commercial cream.

The stability of the commercial cream remained high when it was mixed with the emulsion. Mixing the cream with the emulsion increased its yield resistance. However, this resistance decreased considerably if the amount of emulsion in the mixture was increased by more than 1/3 of emulsion, probably due to a breakage of the structure.

The behavior of commercial cream was predominantly elastic, while double emulsion presented a predominantly viscous character. The mixture with just 1/4 of emulsion presented a behavior similar to cream, while the addition of 1/2 of emulsion produced a change in behavior closer to the one registered for double emulsion alone, with the behavioral intermediate being when 1/3 of emulsion was added.

It has been demonstrated the feasibility to incorporate concentrated double emulsions containing resveratrol into a commercial cream, obtaining a cream with resveratrol concentration up to 0.0042 mg/g and suitable physical properties for satisfactory consumer use.

Author Contributions: R.D.-R., investigation, data curation, and writing—original draft preparation; L.M.-R., investigation and data curation; A.L., data curation, contextualization, supervision, and writing—review and editing; I.M., investigation, data curation and contextualization, M.M., data curation, conceptualization, visualization, writing—review and editing, and funding acquisition; G.G., conceptualization, supervision, writing—review and editing, and funding acquisition. All authors have read and agreed to the published version of the manuscript.

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