VEGETABLE OIL-BASED MICROEMULSIONS WITH DERMATO-COSMETIC APPLICATIONS

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Microemulsions are optically isotropic and thermodynamically stable systems, composed of an oily phase, water, a surfactant, and/or a co-surfactant. For topical cosmetic actives delivery, microemulsions are suitable.

The aim of this work was to develop and characterize biocompatible microemulsions as delivery systems for dermato-cosmetics actives, by using grape seed oil as the oily phase and a blend of highly biocompatible nonionic surfactant and co-surfactant for stabilization. Tween 80 was used as the surfactant because it is safe as a cosmetic ingredient and 1-octanol as the co-surfactant.

The obtained systems were physico-chemically characterized, using dynamic light scattering, electrical conductivity and rheometric measurements.

Keywords: dermal actives delivery; microemulsion; biocompatibility

1. Introduction

The development of an ideal vehicle for delivery of different cosmetic actives in skin is currently a hot topics attracting substantial interest [1]. Significant efforts have been made in order to ensure effective cosmetic actives delivery into the dermal layer of the skin, and much attention has been paid to reduce the particle size of the dispersed phase [2]. From this point of view, microemulsions are suitable colloidal vectors for topical cosmetic formulations and represent efficient transport systems [3]. They are transparent, translucent and thermodynamically stable systems, composed of an oily phase, water, a surfactant, and/or a co-surfactant, with droplet size between 1- 100 nm [4,5]. These colloids are classified in Winsor -I, -II, -III and –IV (W-I, -II, -III and –IV), according to the phases separated. For medical or cosmetic use, single phase (W IV type) microemulsions are of interest. W IV microemulsions may exhibit either

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corpuscular (oil-in-water O/W, water-in-oil W/O) or bicontinuous structures. One major advantage is that microemulsions increase solubility of bioactives and protect solubilized actives from degradative reactions [6]. Some basic compositions of microemulsions with dermal use that contain cosmetic actives are listed in Table 1.

Table 1

Examples of microemulsions with cosmetic actives, that act as delivery systems

Surfactant/Co-surfactant mixture	Oil phase	Aqueous phase	Cosmetic active	Reference
Labrasol/Plurol Oleique	Medium chain triglycerides	Water	Ascorbyl palmitate	[7]
PEG-20 glycerol monooleate/Poloxamer/ propylene glycol	Pelemol BIP	Water	Curcumin	[3]
Decylglucoside/Propylene glycol	Isopropyl myristate	Water	α-tocopherol and lipoic acid	[8]
Tween 80/Propylene glycol	Isopropyl myristate	Water	Salicylic acid	[9]
Brij/Propylene glycol	mono/di/triglycerides of capric and caprylic acids	Water	Lycopene	[10]

The purpose of this work was to develop and characterize biocompatible microemulsions as delivery systems for dermato-cosmetic actives, using grape seed oil as the oily phase and a blend of highly biocompatible nonionic surfactant and co-surfactant for stabilization. The grapeseed oil employed here was obtained by the cold pressing method, and is rich in Vitamin E. It contains mainly linoleic acid that fortifies the skin barrier. Grapeseed oil is a highly biocompatible oil that moisturizes and balances the skin, reduces inflammation, and minimizes fine lines and wrinkles [11, 12]. Despite these excellent properties, there are only a few papers in literature dealing with the preparation, characterization and uses of nano- and microemulsions based on grapeseed oil [13, 14, 15]. In comparison with other vegetable oils, grapeseed oil contains powerful antioxidants and is suitable for sensitive skin, thus making the final formulation suitable for dermato-cosmetic uses. Also, taking into consideration the costs, grapeseed oil is advantageous economically because it's extracted from a waste. This vegetable oil was chosen as the oily phase in our microemulsion system due to its intrinsic cosmetic beneficial properties and also because it can act as a delivery system for other active components, for example some hydrophobic cosmetic actives. As a cosmetic active, curcumin was loaded into a selected microemulsion system. Curcumin, which is a compound isolated from turmeric, has attracted a large interest in recent years because of its various biological properties and lack of toxicity and is being researched for cosmetic applications. Thus, curcumin protects skin by eliminating free radicals and reducing inflammation, improves

collagen deposition, increases fibroblast and vascular density and reduces wrinkles. Curcumin treatment also decreased wound-healing time, and it is useful in psoriasis and skin cancer treatment [16, 17]. In order to prepare biocompatible microemulsions, Tween 80 was used as a nonionic surfactant, as it is safe as a cosmetic ingredient [18], while octanol, which is used in pharmaceutical industry as a chemical skin penetration enhancer, was employed as a co-surfactant [19]. Several microemulsion formulations were designed and tested. Phase diagrams were obtained and all W IV microemulsions were characterized using dynamic light scattering, electrical conductivity test and rheometric measurements. Microemulsions containing curcumin were also prepared from formulation selects based on the pseudoternary phase diagrams.

In the present work the possibility to obtain single phase microemulsions with Grapeseed oil instead of synthetic oils such as isopropyl myristate, silicones or fatty acids, and using Tween80 / octanol (S_{mix}) as the surfactant mixture was investigated for the first time.

2. Materials and Methods

2.1. Materials

The grapeseed oil obtained by the cold pressing method, of commercial grade (MAYAM Cosmetics), Tween 80 (SIGMA-ALDRICH) and 1-octanol (>99% purity, MERCK) were used as received. Distilled water was employed in all experiments.

2.2. Microemulsion preparation

Microemulsions were prepared using three mass ratio combinations between surfactant and co-surfactant, namely 1/1, 1/2 and 2/1. For every S_{mix} combination, three levels of concentrations 84.21%, 75.65% and 66.67% were initially achieved, resulting 9 sets of colloidal systems named: MOC; MOC3; MOC4; MOC5; MOC6; MOC7; MOC8; MOC9; MOC10 (Table 2). For each set the amount of water was varied to obtain 0.5:1; 1:1; 1.5:1; 2:1; 2.5:1; 3:1; 3.5:1; 4:1; 4.5:1; 5:1 and 6:1 water:oil mass ratios. This way, the ranges of variation of components were 50-84.21% for S_{mix}, 5.26-40% for water and 9.09-22.22% for oil. The prepared samples were evaluated by simple observation and the ones considered microemulsions (optical isotropic appearance) are summarized in Table 2. The microemulsion components were homogenized by means of an ULTRA-TURRAX equipment, and then the mixtures were left 24-48 h at 25 °C to allow for the necessary equilibration time. For the prepared microemulsions pseudoternary phase diagrams were made by using the Triplot 4.1 software.

2.3. Characterization of microemulsions

The formation of W I, -II, -III, -IV microemulsions was visually assessed. Due to the fact that only the W IV microemulsions are of interest in this study,

only these ones were physically characterized. The microemulsion droplet size was determined by dynamic light scattering (DLS) by means of a Nano ZS ZEN3600 Zetasizer (Malvern Instruments, UK) equipment. The conductivity measurements were carried out on undiluted samples by employing a Cole-Parmer conductivity meter model 500. The viscosity measurements were run on a Kinexus Pro rheometer (Malvern Instruments, UK) with 1.60 software for data acquisition, equipped with a Peltier element for temperature control. All measurements were performed in rotational mode by using a 1°/40 mm cone plate, at 25 °C, with 5-minute equilibration time. A share rate between 0.5 and 1000 s^{-1} was applied for all measurements.

3. Results and Discussions

3.1. Formulations and pseudoternary phase diagrams construction

In the present study, the water-oil-surfactant-co-surfactant mixtures were prepared and after a short period of stirring, microemulsions spontaneously formed. Pseudoternary phase diagrams were constructed to define the area of the microemulsion region (Fig. 1). The composition and type of the resulting microemulsions are displayed in Table 2. For some of the compositions tested, W IV microemulsion type resulted (Table 2, Fig. 2). As it is expected, high concentrations of S_{mix} were needed to form microemulsions, while at concentrations lower than 70% macroemulsions were present. The largest microemulsion area resulted for the 1:1 Tween80:octanol mass ratio (Fig. 1). For the 1:2 Tween80:octanol mass ratio, predominantly W I-type microemulsions were obtained and only 3 W IV microemulsions. Therefore, a higher mass proportion of co-surfactant favors the formation of W I microemulsion type. Most W IV microemulsions were obtained for the 1:1 surfactant:co-surfactant mass ratio. Using a 2:1 Tween80:octanol mass ratio the smallest microemulsion area resulted, and not only W IV type microemulsions formed, but also W II-type microemulsions were obtained. Therefore, the decrease of the cosurfactant proportion in the S_{mix} negatively influenced the formation of the microemulsions. This fact confirms that for microemulsion systems the surfactant/co-surfactant ratio is the most important parameter. In this study 1% of curcumin was encapsulated in the microemulsion with 1/1 surfactant:co-surfactant mass ratios, with 69.97 % S_{mix} and 1/1 water:oil mass ratio.

Encapsulation of the selected active principle was made by adding the curcumin powder into the microemulsion 1MOC7, followed by magnetical stirring for 24 h. According to data from literature, the solubility of curcumin in different vegetable oils is between 0.4 and 0.6 (mg/g) [20]. But in 1 g of the selected microemulsion 10 mg of curcumin were loaded, confirming that our microemulsions have the capacity to incorporate relatively large quantities of active principles.

Table 2

Composition, type, structure and electrical conductivity of the microemulsions

No.	Sample	Concentration of Tween80 + octanol (% wt)	Water:Oil mass ratio	Tween80: octanol mass ratio	Microemulsion type	Electrical Conductivity (μS/cm)	Structure of the microemulsion
1	0.5 MOC5	84.21	0.5	1:1	W IV	4.66	W/O
2	1 MOC5	80.00	1	1:1	W IV	7.4	W/O
3	1.5 MOC5	76.19	1.5	1:1	W IV	10.5	W/O
4	2 MOC5	72.73	2	1:1	W IV	26.4	bicontinuous
5	2.5 MOC5	69.56	2.5	1:1	WIV	67	bicontinuous
6	3 MOC5	66.66	3	1:1	W II	-	-
7	3.5 MOC5	64.00	3.5	1:1	W IV	63	bicontinuous
8	4 MOC5	61.54	4	1:1	W IV	356	O/W
9	4.5 MOC5	59.00	4.5	1:1	W II	-	-
10	5MOC5	57.00	5	1:1	W IV	340	O/W
11	0.5 MOC7	75.65	0.5	1:1	W IV	6	W/O
12	1 MOC7	69.97	1	1:1	W IV	16.1	bicontinuous
13	1.5 MOC7	65.54	1.5	1:1	W IV	71.1	bicontinuous
14	2 MOC7	60.84	2	1:1	W IV	54.4	bicontinuous
15	0.5 MOC9	66.67	0.5	1:1	W IV	3.61	W/O
16	1 MOC9	60.00	1	1:1	W IV	58.7	bicontinuous
17	0.5 MOC3	84.21	0.5	1:2	W IV	5.13	W/O
18	1 MOC3	80.00	1	1:2	W IV	3.64	W/O
19	1.5 MOC3	76.19	1.5	1:2	W I	-	-
20	2 MOC3	72.73	2	1:2	W I	-	-
21	0.5 MOC4	75.69	0.5	1:2	W IV	2.08	W/O
22	1 MOC4	70.00	1	1:2	W I	-	-
23	1.5 MOC4	65.13	1.5	1:2	W I	-	-
24	0.5 MOC	66.67	0.5	1:2	W I	-	-
25	1 MOC	60.00	1	1:2	W I	-	-
26	1.5 MOC	54.55	1.5	1:2	W I	-	-
27	2 MOC	50.00	2	1:2	W I	-	-
28	0.5 MOC8	84.21	0.5	2:1	W IV	6.97	W/O
29	1 MOC8	80.00	1	2:1	W II	-	-
30	1.5 MOC8	76.56	1.5	2:1	W IV	16.11	bicontinuous
31	2 MOC8	72.73	2	2:1	W IV	26.8	bicontinuous
32	0.5 MOC10	75.65	0.5	2:1	W II	-	-
33	1 MOC10	69.97	1	2:1	W IV	17.13	bicontinuous
34	1.5 MOC10	65.54	1.5	2:1	W IV	43.7	bicontinuous
35	2 MOC10	60.84	2	2:1	W II	-	-

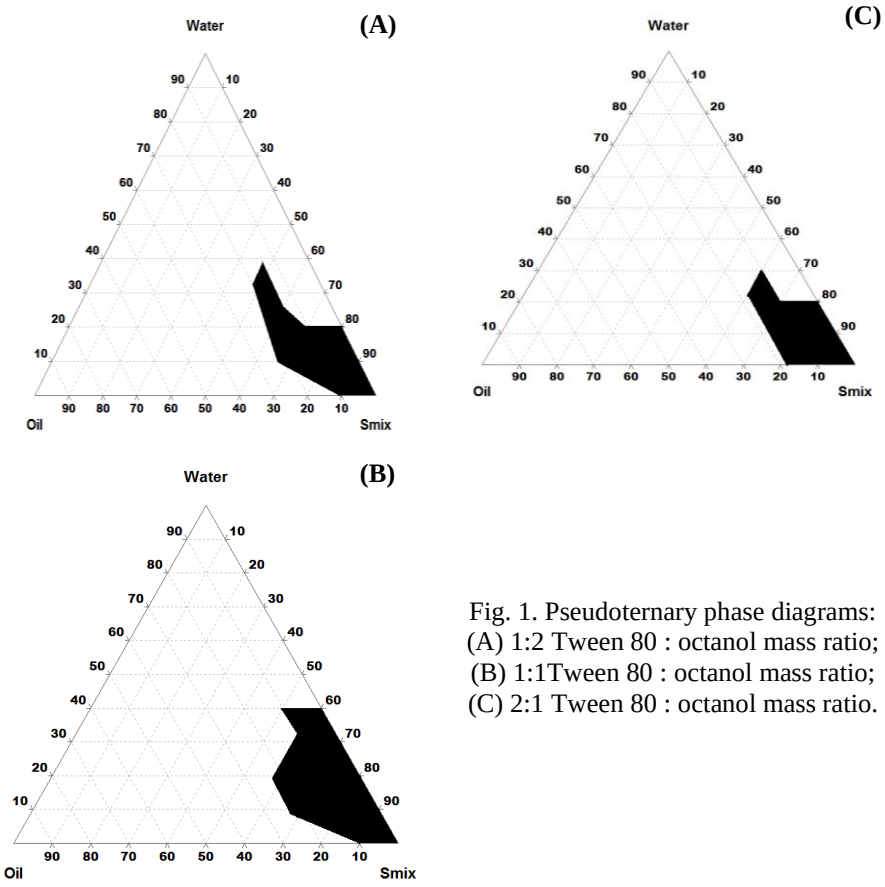

Fig. 1. Pseudoternary phase diagrams:
(A) 1:2 Tween 80 : octanol mass ratio;
(B) 1:1Tween 80 : octanol mass ratio;
(C) 2:1 Tween 80 : octanol mass ratio.

Fig. 2. Appearance of the W IV microemulsions.

3.2. Structure of the W IV microemulsions

In order to characterize the structure of the W IV microemulsions (O/W or W/O or bicontinuous), conductivity and droplet size measurements are necessary besides the composition data. Conductivity is an important characteristic of microemulsions, providing information about the structural state of the system. In a set of samples with the same initial composition by increasing the water weight

fraction the conductivity also increases. Low conductivity values are characteristic for W/O microemulsions, because of the discrete water droplets content and the non-conducting continuous oil phase. By increasing the water weight fraction, conductivity increases because of the increasing water presence in the continuous phase. The sharp increase of conductivity indicates phase inversion from W/O microemulsion to O/W microemulsion [21, 22]. Therefore, the electrical conductivity of the obtained W IV microemulsions was measured, the results being displayed in Table 2. Based on the recorded conductivity values, the single phase microemulsions were classified in W/O, bicontinuous and O/W microemulsions (Table 2). The Structure of the W IV microemulsions was established based on a method described in literature (Fig. 3) [23, 24, 25,]. As conductivity measurements are susceptible to the water fraction in the sample, the relation between the water weight percentage and electrical conductivity values were studied by observing the slope change. Thus, Fig. 3 displays the variation of the conductivity values as a function of the weight percentage of water for the MOC5 set of microemulsions, and the change of the slope as a result of the microemulsion structure modifications from W/O microemulsion to bicontinuous microemulsions and then from bicontinuous microemulsions to O/W microemulsions. The bicontinuous to O/W microemulsions transition was observed just for the MOC5 microemulsions set. In the case of the other experimental sets, the insufficient number of W IV microemulsions prevented us to apply the same method as for the MOC5 set. For these W IV microemulsions, having a composition similar to those in the MOC5 set, the structure was assigned based on the electrical conductivity values and structure classification for MOC5 set microemulsions (Table 2, Fig. 3).

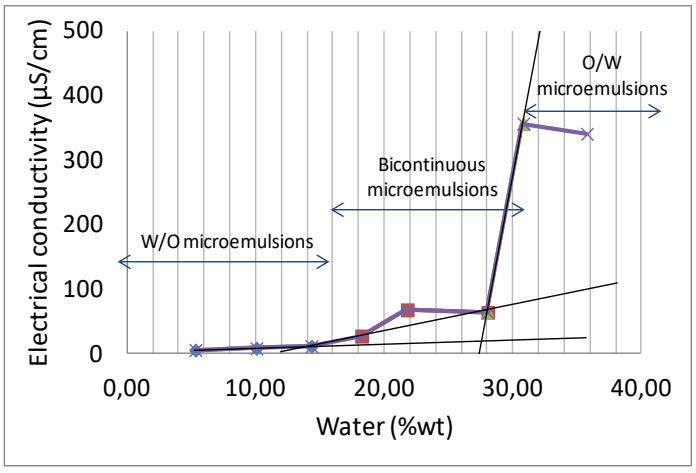

Fig. 3. Conductivity of the MOC5 set microemulsions as a function of weight percentage of water

DLS measurements allowed us to determine the size of the droplets existing in the continuous phase, i.e. water droplets in the continuous oily phase or oil droplets in the continuous aqueous phase. Droplet size distributions of the discontinuous phase of microemulsions are shown in Figs. 4-6. The results indicate that the samples with the lowest and the highest water content (0,5MOC5; 1MOC5; 0,5MOC3; 0,5MOC8; 4MOC5; 5MOC5) displayed the smallest size of the discontinuous phase droplets (about 10-25 nm). The discontinuous phase size of the rest of the samples had around 250 nm because of the larger water content that made posible interconections between an increased number of water droplets, resulting in the formation of continuous water domains intercalated with continuous oil phase, phenomenon characteristic to the bicontinuous structures. So, in this type of structures the sample volume is divided into areas displaying a characteristic size and which are filled with oily or aqueous phase [23, 26].

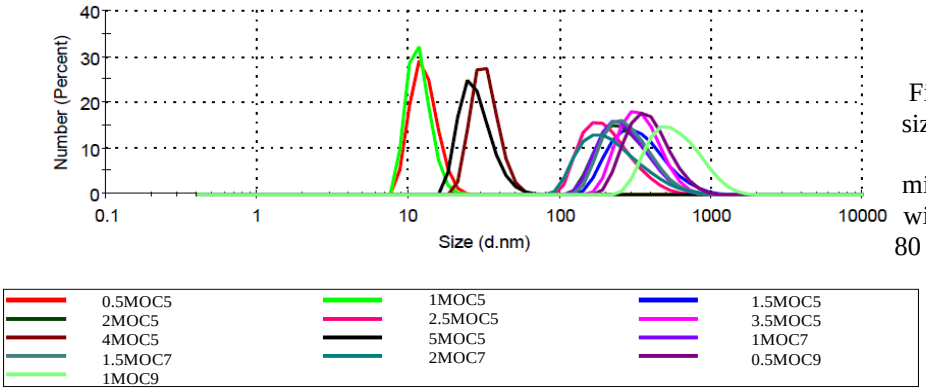

Fig. 4. Droplet size distribution for the microemulsions with 1:1 Tween 80 : octanol mass ratio

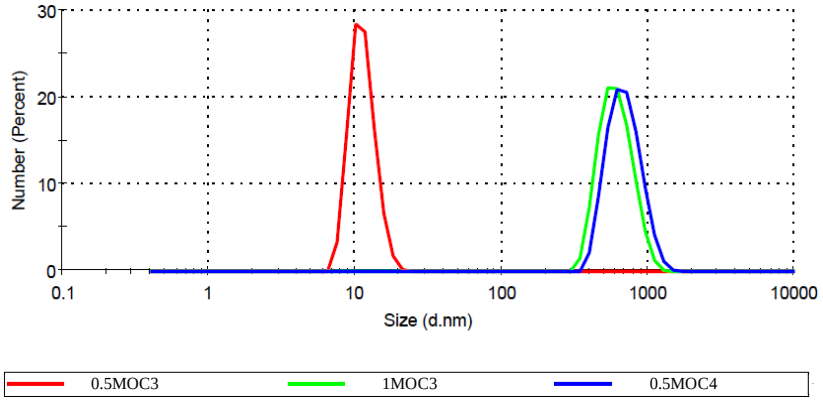

Fig. 5. Droplet size distribution for the microemulsions with 1:2 Tween 80 : octanol mass ratio

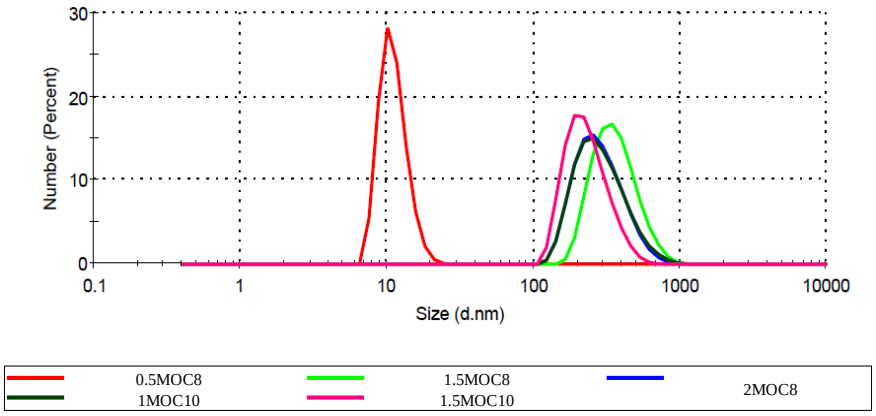

Fig. 6. Droplet size distribution for the microemulsions with 2:1 Tween 80 : octanol mass ratio

3.3. Rheological measurements

Flow curves for all W IV microemulsions, obtained for different concentrations and mass ratios between surfactant and co-surfactant are shown in Fig. 7. Most of the samples showed a Newtonian flow behavior (Fig. 7), meaning that the viscosity of the microemulsions did not depend of the shear rate value. For the samples belonging to the same set and with the same surfactant:co-surfactant mass ratio, microemulsion viscosity increased with increasing water content (Fig. 8).

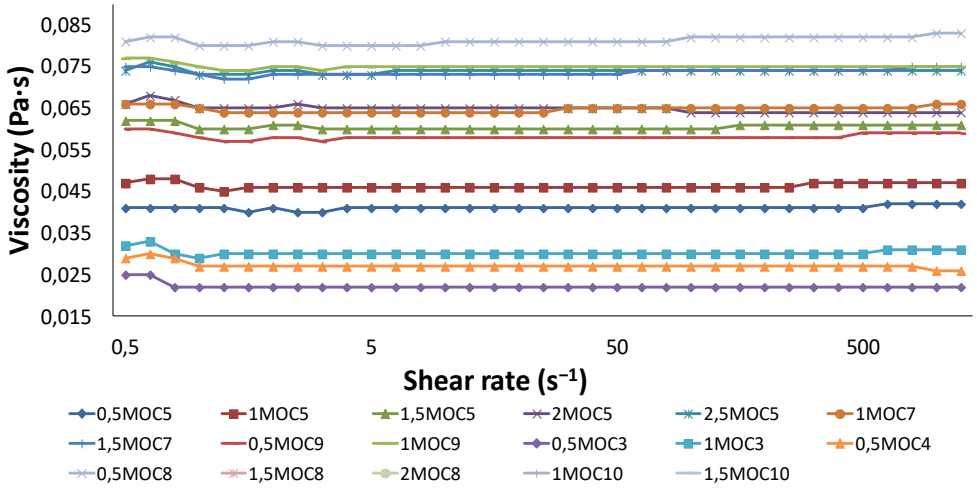

Fig. 7. Flow curves indicating Newtonian behaviour for most W IV microemulsions obtained.

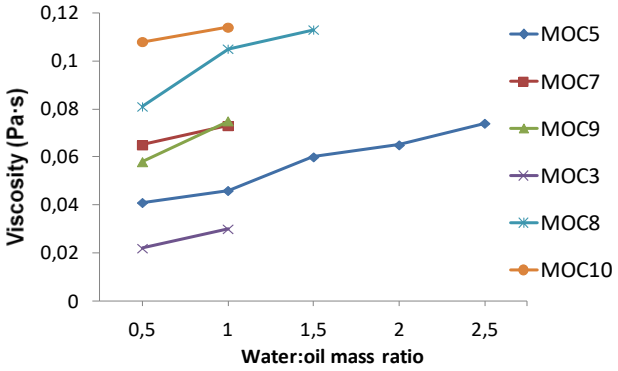

Fig. 8. Viscosity dependence on the Water/Oil mass ratio for different WIV microemulsion sets.

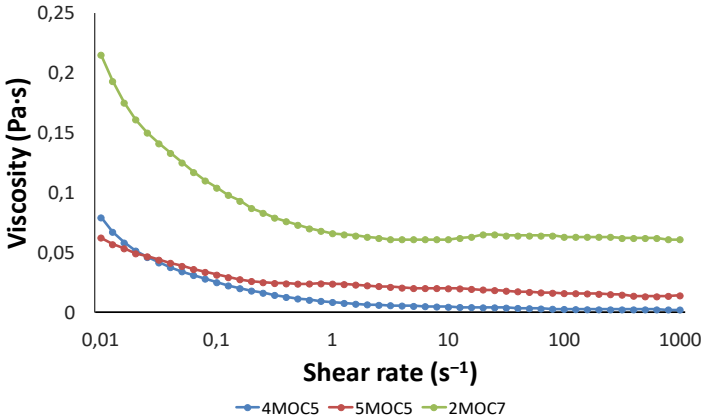

Fig. 9. Flow curves indicating Non-Newtonian behaviour for some of the W IV microemulsions obtained.

Three microemulsions with the highest water content from two sets (2MOC7, 4MOC5 and 5MOC5), exhibited a pseudoplastic non-Newtonian flow behavior (Fig.9), meaning that viscosity decreased with increasing shear rate value. These three samples had gel like appearance, but after applying a minimum force they became liquid. For cosmetic applications, a pseudoplastic non-Newtonian flow behavior is suitable [27]. Due to the higher viscosity at lower shear rates, the microemulsion can be easily applied topically, while the decrease of the viscosity when increasing the shear rate ensures better skin penetration.

4. Conclusions

The preparation and characterization of microemulsions using Tween 80 as surfactant, 1-octanol as co-surfactant and grapeseed oil, a highly biocompatible vegetable oil with many benefits for skin, as oily phase was investigated in order to obtain single phase microemulsions. By varying the mass ratio between the microemulsions components, three pseudoternary phase diagrams were constructed showing that for each Tween80:octanol mass ratio a microemulsion area was obtained, the largest one being obtained for equal amounts of these two components. For concentrations of the surfactant-co-surfactant system lower than

70% only macroemulsions resulted. The largest number of W IV microemulsions were obtained for the 1:1 Tween80: octanol mass ratio, as well. The W IV-type microemulsions were characterized by electrical conductivity, dynamic light scattering and rheometric measurements. The structure of the W IV type microemulsions were established based on conductivity results. We showed that O/W, W/O and microemulsions displaying a bicontinuous structure were obtained. The DLS measurements allowed us to determine the size of the droplets existing in the continuous phase, and revealed the presence of bicontinuous structures for some W IV microemulsions. The rheological measurements indicated a Newtonian behavior for most of the single phase microemulsions, whereas only 3 samples exhibited a pseudoplastic non-Newtonian flow behavior. For similar samples, the viscosity increased with increasing water content. By taking into account the results, the 5MOC5 microemulsion may be recommended for topical cosmetic use as a potential cosmetic actives carrier, because of the small size of the discontinuous oily phase, its rheological behavior and the lowest S_{mix} concentration.

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