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# Characterization of caprylocaproyl macrogolglycerides based microemulsion drug delivery vehicles for an amphiphilic drug

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**Abstract**

Microemulsion systems composed of water, isopropyl myristate, PEG-8 caprylic/capric glycerides (Labrasol®), and polyglyceryl-6 dioleate (Plurol Oleique®), were investigated as potential drug delivery vehicles for an amphiphilic model drug (diclofenac diethylamine). Pseudo-ternary phase diagram of the investigated system, at constant surfactant/cosurfactant mass ratio (Km 4:1) was constructed at room temperature by titration, and the oil-to-surfactant/cosurfactant mass ratios (O/SC) that exhibit the maximum in the solubilization of water were found. This allowed the investigation of the continuous structural inversion from water-in-oil to oil-in-water microemulsions on dilution with water phase. Furthermore, electrical conductivity ($\sigma$) of the system at Km 1:4, and O/SC 0.250 was studied, and the percolation phenomenon was observed. Conductivity and apparent viscosity ($\eta'$) measurement results well described colloidal microstructure of the selected formulations, including gradual changes during their formation. Moreover, $\sigma$, $\eta'$, and pH values of six selected microemulsion vehicles which differ in water phase volume fraction ($\Phi_w$) at the selected Km and O/SC values, were measured. In order to investigate the influence of the amphiphilic drug on the vehicle microstructures, each system was formulated with 1.16% (w/w) diclofenac diethylamine. Electrical conductivity, and $\eta'$ of the investigated systems were strongly affected by drug incorporation. The obtained results suggest that diclofenac diethylamine interacts with the specific microstructure of the investigated vehicles, and that the different drug release kinetics from these microemulsions may be expected. The investigated microemulsions should be very interesting as new drug carrier systems for dermal application of diclofenac diethylamine.


*Keywords:* Microemulsion; Caprylocaproyl macrogolglycerides; Percolation; Drug delivery; Diclofenac diethylamine

## 1. Introduction

Microemulsion systems, owing to their pharmaceutical advantages (thermodynamic stability, ease of preparation, transparency, low viscosity, considerable potential for solubilizing variety of drugs) are the object of investigations in relation to drug delivery. In spite of numerous advantages in comparison with other colloidal vehicles, microemulsions often require a high content of surfactant that can lead to skin irritation (Kumar and Mital, 1999; Lawrence and Rees, 2000). The concentration of surfactant can sometimes be reduced by the addition of cosurfactants (Sagitani and Friberg, 1980). The majority of the work reported in the scientific literature concerns microemulsion systems based on pharmaceutically unacceptable cosurfactants such as short- or medium-chain alcohols (Kumar and Mital, 1999; Lawrence and Rees,

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2000). The good biological acceptance of non-ionic surfactants (Kibbe, 2000) as well as ability to form microemulsions that are insensitive to pH and electrolyte concentration are the main motives for their extensive use (Kumar and Mital, 1999; Lawrence and Rees, 2000). It has been recently reported that certain mixtures of non-ionic surfactants can provide enhancement of solubilization of water in water-in-oil microemulsions (Hiuberts and Shah, 1997; Sagitani and Friberg, 1980). There have been several studies involving low-irritant caprylocaproyl macrogolglycerides based microemulsions as drug delivery vehicles for topical application (Gašperlin and Špiclin, 2001; Delgado-Charro et al., 1995; Kreilgaard, 2001). In order to facilitate caprylocaproyl macrogolglycerides based microemulsions formation, the surfactants based on polyglycerol fatty acid esters have been used as cosurfactants (Gašperlin and Špiclin, 2001; Delgado-Charro et al., 1995; Kreilgaard, 2001). All the same, it has been recently reported that caprylocaproyl macrogolglycerides based microemulsion systems incorporating isopropyl myristate as oil phase, have a large microemulsion region in their phase diagrams (Choi et al., 1997).

Due to the variety of structures occurring in them (water-in-oil (W/O), oil-in-water (O/W), or bicontinuous structures in which water continuous and oil continuous domains are separated by surfactant monolayers), microemulsions display a rich behavior regarding the release of solubilized material. Also, one can reach sustained release if the interactions between drug and surfactant and/or partitioning of the drug between oil and water phases strongly affect the drug release (Kumar and Mital, 1999). In order to investigate a drug delivery potential of microemulsion vehicles, it is necessary to characterize their microstructure as well as a microstructure of drug loaded microemulsions. The formation process and gradual changes in microemulsion microstructure can be monitored quantitatively by measuring the electrical conductivity and rheological properties of system (Kumar and Mital, 1999; Lawrence and Rees, 2000). Apart from the microemulsion structure and composition, the incorporated drug molecules participate in the microstructure of the system and may influenced it due to molecular interactions, especially if the drug possesses amphiphilic and/or mesogenic properties (Müeller-Goymann et al., 1995). Diclofenac diethylamine is a nonsteroidal anti-inflammatory drug able to form micelles and lyotropic liquid crystals in water (Kriwet and Müeller-Goymann, 1993). The interactions of diclofenac diethylamine with phospholipids have been reported (Engehausen and Müeller-Goymann, 1992). Such interactions between drug molecule and components of pharmaceutical formulations may strongly influence drug release (Müeller-Goymann et al., 1995; Kriwet and Müeller-Goymann, 1993).

There were three specific objectives in the present study. First, we wanted to formulate different types of microemulsion vehicles stabilized with a minimum amount of caprylocaproyl macrogolglycerides/polyglyceril-6 dioleate mixture in order to obtain low-irritant microemulsion vehicles for cutaneous application. Second, we wanted to investigate the gradual changes in the microstructure with the addition of water phase into the mixture of oil and surfactants during the preparation of the microemulsions. Third, we have investigated the influence of diclofenac diethylamine on the stability, optical texture, conductivity, and rheological properties of the selected microemulsion formulations.

## 2. Materials and methods

### 2.1. Materials

PEG-8 caprylic/capric glycerides (Labrasol®) and polyglyceryl-6 dioleate (Plurol Oleique®) were a kind gift from Gattefosse (Lyon, France). Isopropyl myristate was supplied by Cognis GmbH (Düsseldorf, Germany). Water was purified by double distillation in a glass apparatus and then deionized using Millipore Milli-Q® Water System (Millipore Corporation, Bedford, USA). Diclofenac diethylamine was a kind gift of Hemofarm a.d. (Vrsac, Yugoslavia). All substances were used as received without further purification.

### 2.2. Microemulsion preparation

#### 2.2.1. Construction of phase diagram

The pseudo-ternary phase diagram was constructed by titration of homogenous liquid mixtures of oil, surfactant, and cosurfactant, with water at room temperature (Gattefossé, 1994). Labrasol®, the surfactant

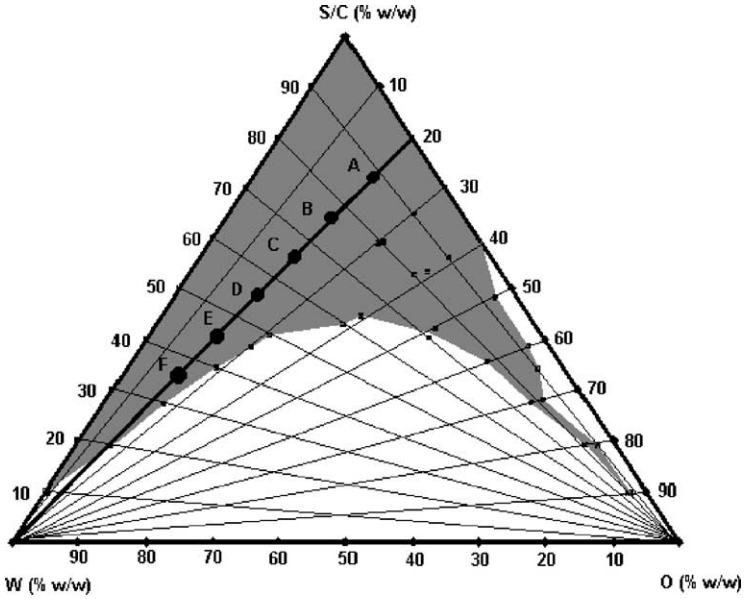


Fig. 1. Pseudo-ternary phase diagram with the microemulsion existance region (the shaded area) of water (W)/PEG-8 caprylic/capric glycerides (S)/polyglyceryl-6 dioleate (C)/isopropyl myristate (O) system at Km 4:1. Diagram was studied at room temperature. The selected O/SC 0.250 represents the continuous changes in the investigated systems compositions (A–F) during their formation.

(S), and Plurol Oleique®, the cosurfactant (C), were weighed in the same screw-cap dark-brown glass vial, vortexed vigorously for 1 h, and then stored overnight at room temperature. At Km 4:1 mixtures of oil phase (O), and surfactant/cosurfactant blend were prepared, where contents of oil and amphiphile blend in the mixtures were varied from 9:1 to 1:9. Water phase was added drop by drop, under magnetic stirring, to each oily mixture. During the titration, samples were stirred to allow equilibration. Following the addition of aliquot of water the mixture was visually examined for transparency. The changes in the sample visual aspect from turbid to transparent and inversely were observed. Transparent, single-phase, low viscous mixtures were designated as microemulsions. After the water titration, in order to establish the microemulsion region borders, titration of water and surfactant/cosurfactant mixtures with oil were performed, in the same manner.

### *2.2.2. Selection of microemulsion formulations for detailed studies*

For further studies, from the constructed pseudo-ternary phase diagram, one initial isopropyl myristate/Labrasol®/Plurol Oleique® mixture with O/SC 0.250 was selected (Fig. 1). Furthermore, six potential microemulsion vehicles (refereed to as A–F in Table 1 and Fig. 1) different from each other by $\Phi_w$, were selected and prepared at Km 4:1 and O/SC 0.250. For the preparation of the microemulsion vehicles appropriate quantities of Labrasol®, Plurol Oleique®, isopropyl myristate, and water were weighed into the screw-cap glass vial. The mixtures were stirred with a magnetic bar to speed up the formation of the transparent systems, at room temperature. Transparent, single-phase formulations were formed in a few seconds. Furthermore, in order to evaluate their drug delivery potential for an amphiphilic model substance, diclofenac diethylamine was dissolved into preweight vehicles at

Table 1
Microemulsion vehicle compositions (% (w/w))

| | A | B | C | D | E | F |
|---|---|---|---|---|---|---|
| Water | 10.0 | 20.0 | 30.0 | 40.0 | 50.0 | 60.0 |
| Isopropyl myristate | 18.0 | 16.0 | 14.0 | 12.0 | 10.0 | 8.0 |
| Labrasol®/Plurol Oleique® | 72.0 | 64.0 | 56.0 | 48.0 | 40.0 | 32.0 |

a concentration ratio of 1.16% (w/w). Both, unloaded and drug-loaded microemulsions were prepared 48 h before investigations (we can reasonably assume that the drug distribution among the oil, water and surfactant micelles, attains the termodynamic equilibrium) and stored at room temperature.

### 2.3. Microemulsion characterization

#### 2.3.1. Polarized light microscopy

Both, unloaded and drug-loaded vehicles were examined by polarized light microscopy (Aus Jena polarizing microscope, Carl Zeiss, Oberkochen, Germany) in order to determine optical isotropy of the samples. The observing whether the sample rotates the plane of polarization of polarized light is very useful tool to distinguish isotropic microemulsions from anisotropic lamellar and hexagonal mesophases.

#### 2.3.2. Centrifugation

In order to eliminate metastable systems, the selected microemulsion vehicles as well as drug-loaded microemulsions were centrifugated (Sigma 2–16 centrifuge, Sigma Laborzentrifugen GmbH, Osterode, Germany) at 13,000 $min^{-1}$ for 30 min.

#### 2.3.3. Conductivity measurements

The solubilization of water phase in the selected oily mixture was monitored quantitatively by measuring the electrical conductivity. The water phase was added drop by drop in the initial mixture of oil and amphiphiles, and measured $\sigma$ of formulated samples, using a conductometer CDM 230 (Radiometer, Copenhagen, Denmark), at $20 \pm 2\,^{\circ}C$ and the frequency of 94 Hz. Additionally, the conductivity of microemulsion vehicles and drug-loaded microemulsions was measured.

#### 2.3.4. Rheological measurements

Rheological behavior of the unloaded and drug-loaded microemulsions was evaluated using a rotational rheometer coupled with cup and bob measuring device (Rheolab MC120, model Z3 DIN, Paar Physica, Stuttgart, Germany). Apparent viscosity data at shear rate ($\gamma$) 200 $s^{-1}$, were obtained at $20 \pm 1\,^{\circ}C$. Experiments were carried out in triplicate for each sample, and results were presented as average ± S.D.

#### 2.3.5. pH

The pH values of the samples were measured by a pH meter (model HI 8417, Hanna Instruments Inc., Woonsocket, USA), at $20 \pm 1\,^{\circ}C$.

#### 2.3.6. Partition coefficient

The drug partition coefficient ($K_p$) at $20 \pm 1\,^{\circ}C$ was calculated according to the concentration of drug remained in water phase of water/isopropyl myristate system after 72 h. Diclofenac diethylamine concentration was determined spectrophotometrically at 275.1 nm (Spectrophotometer Carry 50, Varian, Germany).

## 3. Results and discussion

### 3.1. Phase behavior

Pseudo-ternary phase diagram of the investigated quaternery system water/caprylocaproyl macrogolglycerides/polyglyceryl-6 dioleate/isopropyl myristate is presented in Fig. 1. Formation of microemulsion systems (the shaded area) was observed at room temperature. Phase behavior investigations of this system demonstrated the suitable approach to determine the water phase, oil phase, surfactant, and cosurfactant concentrations for which the transparent, one-phase, low-viscous systems form. During the addition of water in the selected oily mixtures there was continuous transition from oil-rich systems (right side of phase diagram) to water-rich systems (left side of phase diagram). The obtained results show that the maximum solubilization of water was achieved in the oil/surfactant/cosurfactant mixtures with O/SC < 0.250. The maximum percentages of water phase were 75.83% (w/w) for O/SC 0.250 (the content of surfactant/cosurfactant mixture was 19.34% (w/w) and 89.64% (w/w) for O/SC 0.111 (the concentration of amphiphiles mixture was 9.32% (w/w)). With the reduction of an amphiphiles content (O/SC > 0.250) the oil/surfactant/cosurfactant mixtures were less able to solubilize the water phase. Additionally, we have been investigated the structural changes in the selected system with increasing $\Phi_w$ at constant O/SC 0.250, in order to ascertain whether any relationship exists between both the electroconductive behavior and viscosity, and microstructure. Furthermore, from

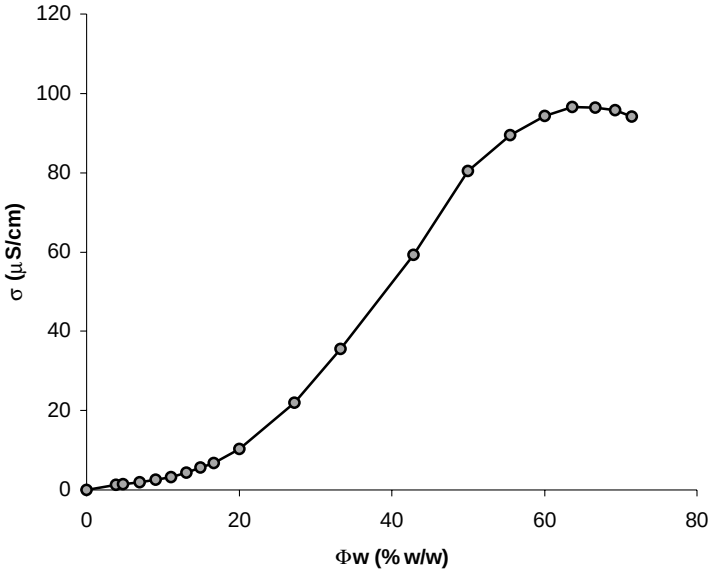


Fig. 2. Electrical conductivity ($\sigma$) as a function of water phase volume fraction ($\Phi_w$) in the system with O/SC 0.250 and Km 4:1.

the above-mentioned investigations, six potential microemulsion vehicles (A–F) were selected. The Km and O/SC values were constant, but the percentages of surfactant/cosurfactant mixture as well as water and oil phases of the vehicles were different, and it was reasonably to expect the different types of colloidal microstructure.

### *3.2. Conductivity measurements and apparent viscosity*

The electrical conductivity of the selected oily mixture, as a function of $\Phi_w$, is presented in Fig. 2. According to obtained conductivity data, the investigated microemulsions can be designed as a type of systems where the $\sigma$ is fairly high and varies with $\Phi_w$. The electrical conductivity of the selected oily mixture was almost zero as long as the $\Phi_w$ was smaller than 10% (w/w). During the water titration up to $\Phi_w \approx 50\%$ (w/w), $\sigma$ increases fast. At $\Phi_w > 50\%$ (w/w), the conductivity of the system was no significantly affected by the further addition of water. It has been previously demonstrated that there is a strong correlation between specific structures of microemulsion systems composed of ionic surfactants, and their electroconductive behavior (Bennett et al., 1982; Borkovec et al., 1988; Clausse et al., 1987; Kahlweit et al., 1987; Lagues, 1979; Strey, 1996). While the water volume fraction increases, the electrical conductivity of these systems slightly increases as well until the critical $\Phi_w$ is reached when a sudden increase in conductivity is observed. This phenomenon is known as percolation, and the critical $\Phi_w$ at which it is occurs is known as percolation threshold ($\Phi_p$) (Bennett et al., 1982). The investigated microemulsion system, containing non-ionic amphiphiles, exhibited electroconductive behavior in spite of its non-ionic type. In the region of low water contents a W/O microemulsion is formed. Beyond the percolation threshold ($\Phi_p \approx 10\%$ (w/w)) conductivity increases linearly and sharply up to $\Phi_w \approx 50\%$ (w/w). It can be concluded that beyond $\Phi_p$ a network of conductive channels exists, which corresponds to the formation of water cylinders or channels in an oil phase due to the attractive interactions between the spherical microdroplets of water phase in the W/O microemulsion. For the $\Phi_w > 50\%$ (w/w) the electrical conductivity increases non-linearly up to a maximum at $\Phi_w \approx 60\%$ (w/w). After the maximum, conductivity of the system was slightly decreased by the further addition of water phase, and these conductivity data can be explained by the dilution of O/W microemulsion with the added water which decreased the concentration of the dispersed oil droplets. Thus, the $\sigma$–$\Phi_w$ curve illustrates the occurrence of the three struc-

Table 2
Electrical conductivity ($\sigma$), apparent viscosity ($\eta'$), and pH of the unloaded vehicles A–F, and the vehicles loaded with diclofenac diethylamine (1.16% (w/w)) studied

| Formulation | Unloaded vehicles | | | Drug-loaded vehicles | | |
|---|---|---|---|---|---|---|
| | $\sigma$ (μS/cm) | $\eta'$ (mPa s) | pH | $\sigma$ (μS/cm) | $\eta'$ (mPa s) | pH |
| O/SC[a] | – | 86.2 ± 0.0003 | – | – | 88.7 ± 0.0001 | – |
| A | 2.9 | 120.0 ± 0.0005 | 7.13 | 3.8 | 128.0 ± 0.0007 | 7.41 |
| B | 10.3 | 111.0 ± 0.0021 | 7.33 | 23.5 | 112.0 ± 0.0015 | 7.45 |
| C | 27.2 | 91.6 ± 0.0005 | 7.62 | 62.1 | 92.0 ± 0.0005 | 7.70 |
| D | 52.5 | 78.1 ± 0.0002 | 7.59 | 122.3 | 92.0 ± 0.0005 | 7.65 |
| E | 80.5 | 77.9 ± 0.0001 | 7.49 | 208.5 | 96.0 ± 0.0001 | 7.55 |
| F | 94.3 | 34.7 ± 0.0005 | 7.25 | 285.7 | 55.0 ± 0.0002 | 7.38 |

[a] OSC, mixture of isopropyl myristate, Labrasol®, and Plurol Oleique®.

tural regions: W/O ($\Phi_w$ < 10% (w/w)), nonspherical W/O–bicontinuous–non-spherical O/W (10% (w/w) < $\Phi_w$ < 50% (w/w)), and O/W ($\Phi_w$ > 50% (w/w)).

Correlation between the results of the examination of the phase behavior and the results of conductivity measurements was a good foundation for further analyses of the system structure by applying rheological measurements. The dependence of the apparent viscosity of the investigated formulations on the water phase concentration is shown in Table 2 and Fig. 3. All tested samples were liquids of low viscosity ($\eta'$ $10^1$–$10^2$ mPa s). Obtained $\eta'$–$\Phi_w$ curve shows that $\eta'$ increases from 86.2 to 120 mPa s with increasing $\Phi_w$ from 0 to 10% (w/w). It is well known that increasing of volume fraction of dispersed phase in microemulsions brings to increase of viscosity (Bennett et al., 1982), and it could be expected that viscosity changes reflects a transformation of system microstructure in the function of $\Phi_w$. Initial increase of viscosity with increase of $\Phi_w$ is probably the consequence of attractive interaction and aggregation of droplets of water phase including molecular reorganization on the interface. Position of the maximum $\eta'$–$\Phi_w$ curve is at water phase of about 10% (w/w). Similar increase of viscosity with the change of quantitative relations in the system which leads to forming of the bicontinu-

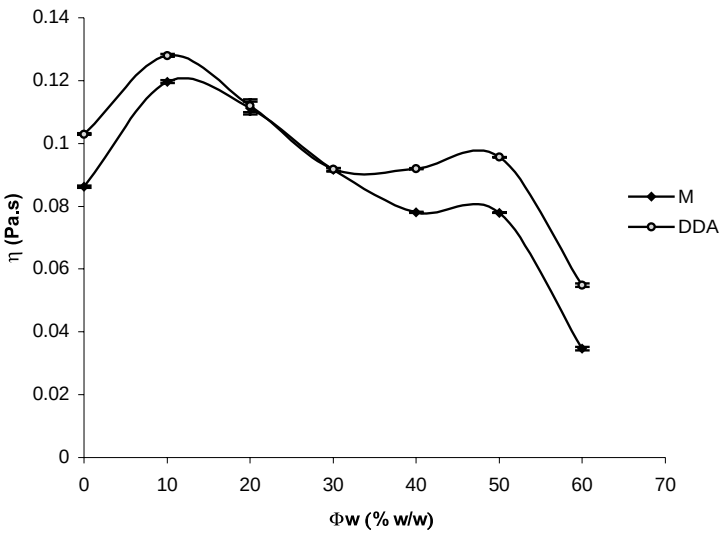


Fig. 3. Apparent viscosity ($\eta'$) of unloaded (M) and drug loaded (DDA) microemulsions as a function of water volume fraction ($\Phi_w$) in the system with O/SC 0.250 and Km 4:1.

ous structure from droplet-like formation is detected at different microemulsion systems which are, till now, investigated. However, bicontinuous structure of liquid microemulsions is more like to be linked to lower value of viscosity (Kahlweit et al., 1987). Measured values of $\eta'$ of this samples decrease from 120 to 34.7 mPa s with increase of water phase concentration from 20 to 60% (w/w). On $\eta'$–$\Phi_w$ curve it can be noted that $\eta'$ decreased very slowly at 20% (w/w)< $\Phi_w$ < 50% (w/w), which probably suggests transformation of system structure from oil continuous (when the water phase content in the system is less than 20% (w/w)), via bicontinuous, to water continuous (when the water phase content in the system is greater than 50% (w/w)). The obtained $\eta'$–$\Phi_w$ curve can be well described by a polynomial equation. Polynomial dependency of viscosity of the system on content of dispersed phase in the system shows the presence of nonspheric aggregates of dispersed phase.

The percolation phenomenon observed in investigated systems as well as rheological measurements results were convincing evidence that system undergoes a structural inversion from oil-continuous to water-continuous over bicontinuous structure as a function of increasing $\Phi_w$, at fixed temperature. Moreover, the electrical conductivity data and viscosity measurements allow us to quantitatively identify bicontinuous structure from droplet microemulsion structures. The molecular origin of this statement is likely the transformation of the interfacial film curvature by the lowering of surfactant/cosurfactant content as well as changing the contents of the water and oil phases. Also, based on the conductivity and viscosity results, the microemulsion system A is W/O type, B, C, and D, are W/O type with nonspherical isolated droplet structure (possibly locally cylindrical) or bicontinuous, and E and F are O/W type.

Furthermore, there have been tested optical texture and stability, and measured pH of the selected formulations. Physico-chemical characterizations were performed on both unloaded and drug-loaded microemulsions. The systems were isotropic, transparent dispersions and after centrifugation no phase separation could be observed. Microemulsion vehicles pH values were in a range of 7.13–7.62 (Table 2). The incorporated drug did not affect the optical texture of the microemulsion formulations and did not influence significantly pH values of the vehicles (Table 2). Diclofenac diethylamine strongly affected electrical conductivity of microemulsion vehicles (Table 2, Fig. 4). Conductivity values for drug loaded microemulsions were increased by about a factor 2–3 in comparison to microemulsions without a drug (Fig. 4). The influence of the active ingredient on the $\eta'$ of the microemulsion formulations is presented in Table 2 and Fig. 3. The $\eta'$ of the drug loaded microemulsions were higher than the unloaded vehicles apparent viscosities. Also, the addition of diclofenac diethylamine changed the bicontinuous regime of the microemulsions microstructure (Fig. 3). The possibility of measuring the drug partition between the oil and the water phases in the presence of the surfactant at the oil–water interface is still an impossible task with common techniques. Thus, the extremely low drug partition coefficient between isopropyl myristate and water phases at $20 \pm 1\,^{\circ}C$ ($k_p$ 0.0708) is useful only to emphasize the very low drug solubility in oil the oil phase. We can assume that at higher water content and lower surfactant and oil concentrations in the system, diclofenac diethylamine is predominantly partitioned between the water phase and a surfactant/cosurfactant interfacial film, contributing the elevated electrical conductivity as well as higher viscosity of bicontinuous microemulsion system. The low p$K_a$ value (p$K_a$ 4.87) (Ledvige and Corrigan, 1998), and latter experimental results suggest that the presence of diclofenac diethylamine in the investigated microemulsion systems increases $\sigma$ due to passage of dethylamonnium cations through channels formed by collision of droplets of water phase. It is known that water solutions of diclofenac diethylamine at room temperature at concentrations above 0.74% form vesicles (critical association concentration at 20 °C is 20 mM; Kriwet and Müeller-Goymann, 1993). Taking the results of examining of partition coefficient it can be supposed that in examined microemulsions with large concentration of water phase came to forming of aggregates of the drug molecules, which reflects on the apparent viscosity of the system. In the formulations which are proved to have cylindrical and bicontinual structure, diclofenac diethylamine is probably located in the interfacial film of tensides and it could not affect the viscosity of the system. In the samples with low water content and high amphiphiles concentrations, diclofenac diethylamine is most likely solubilized in the oil-continuous system.

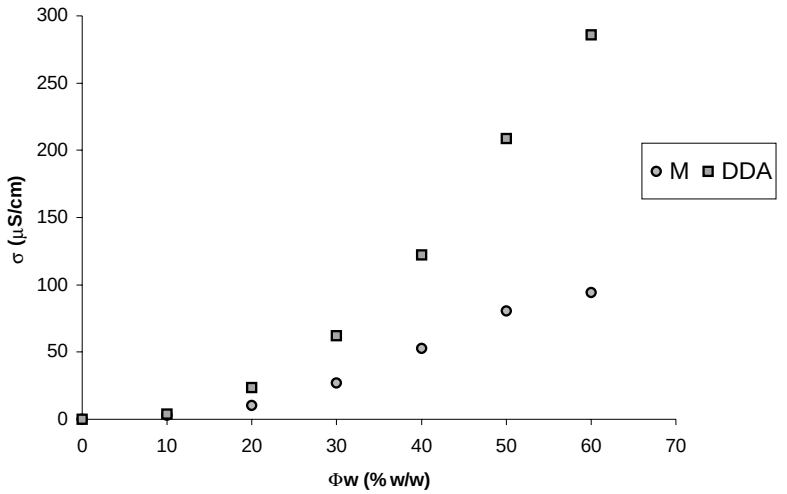


Fig. 4. Electrical conductivity ($\sigma$) of unloaded (M) and drug loaded (DDA) microemulsions.

We demonstrate the relatively simple experimental procedure for screening of the different colloidal vehicles with the specific microstructures that are of great interest for their drug delivery potential. Phase behavior investigations of the system water/PEG-8 caprylic/capric glycerides/polyglyceryl-6 dioleate/ isopropyl myristate, demonstrated the suitable approach to reduce the surfactant content by variation in oil-to-surfactant/cosurfactant mass ratio. Conductivity and viscosity data have confirmed the continuous structural transitions during the increasing of water phase volume fraction in the selected oil/surfactant/cosurfactant mixture. Also, this study demonstrates that diversity of the structures was found in diclofenac diethylamine–water–PEG-8 caprylic/capric glycerides–polyglyceril-6 dioleate–isopropyl myristate microemulsion system. Furthermore, diclofenac diethylamine, due to its amphiphilic properties, influenced significantly the microstructure of the investigated microemulsion vehicles.

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