Scientific paper

The Influence of Microstructure on Celecoxib Release from a Pharmaceutically Applicable System: Mygliol 812®/Labrasol®/Plurol Oleique®/Water Mixtures

Alenka Zvonar,[1] Branka Rozman,[1] Marija Bešter Rogač[2] and Mirjana Gašperlin[1,*]

[1] *University of Ljubljana, Faculty of Pharmacy, Aškerčeva 7, 1000 Ljubljana, Slovenia*

[2] *University of Ljubljana, Faculty of Chemistry and Chemical Technology, Aškerčeva 5, 1000 Ljubljana, Slovenia*

* *Corresponding author: E-mail: mirjana.gasperlin@ffa.uni-lj.si*

Received: 27-10-2008

Dedicated to Professor Josef Barthel on the occasion of his 80th birthday

Abstract

Structural transformations were investigated in unloaded and celecoxib-loaded microemulsions on a dilution line containing, initially, 12 wt. % of Mygliol 812® and 88 wt. % of the surfactant (Labrasol®)/co-surfactant (Plurol Oleique®), 4:1 wt. % mixture. Electrical conductivity, viscosity, surface tension and density measurements revealed that two structural transitions take place along the dilution line studied. At ~27 wt. % of water the oil-continuous (w/o) system converted to a bicontinuous microemulsion and a transition to a water-continuous (o/w) microemulsion followed at ~45 wt. % of water. After incorporation of celecoxib at 1 wt. % concentration the microemulsion remained stable and no change in its microstructure was observed. Celecoxib release was then measured for each type of microemulsion. It was shown to be influenced by the microstructure and solubilization capacity of the system, and can, to a certain extent, be predicted. Stability testing of celecoxib-loaded microemulsions revealed that they are stable over 90 days storage at 40 °C.

Keywords: Microemulsions, microstructure, drug release, stability, celecoxib, solubilization

1. Introduction

Microemulsions are optically isotropic and thermodynamically stable nanosized mixtures of oil, water, and amphiphile(s) that form spontaneously. They usually contain cosolvents or cosurfactants to achieve the low interfacial tension and required packing parameters.[1,2] Due to low interfacial tension between oil and water, a wide range of microemulsion structures is possible. In general, microemulsions can be divided into 3 types: water-in-oil (w/o), bicontinuous, and oil-in-water (o/w). The effective use of microemulsions in many scientific and industrial applications is directly related to an understanding of their microstructure, which is one of the most basic aspects of formulation design. Thus, many studies have been focused on this particular topic.[3–7]

Microemulsions are stable; however they are not inert vehicles. The addition of a drug to pharmaceutical microemulsions may therefore significantly affect their phase behaviour and thus the microstructure and stability of the system.[8] Due to the variety of structures, microemulsions also display diverse behaviour regarding the release of solubilized drug. In order to investigate the drug delivery potential of microemulsion vehicles, it is therefore necessary to characterize the microstructure of drug-free as well as drug-loaded systems. In contrast to the simplicity of microemulsion preparation, characterization of their microstructure is a far from trivial matter and requires a combination of several techniques. Although microemulsions are thermodynamically stable, their microstructure in the bicontinuous region is continuously changing, thus complicating structure determination. Using a number of different methods, such as electrical conductivity, rheology, density, surface tension and differential scanning calorimetry (DSC), it is possible to characterize the internal structure of the microemulsion.[4] Further experi-

mental techniques reported to be used in characterization of these systems include small-angle neutron and X-ray scattering (SANS, SAXS), nuclear magnetic resonance (NMR), fluorescence correlation spectroscopy (FCS) and freeze-fraction transmission electron microscopy (cryo-FESEM).[9–11]

Solubilization of hydrophobic drugs with low aqueous solubility has been a major area of interest in recent years. Most commonly encountered techniques for solubilizing such drugs involve addition of cosolvent or surfactant, pH adjustment and complexation with cyclodextrins. Application of microemulsions has also received attention in this field.[12–16] When a microemulsion is introduced into a physiological environment it can change its structure, due to dilution with physiological fluid. Consequently, the variety of possible structures implies different release rates. It is therefore important to characterize microemulsions that are formed in situ during the dilution step and lie on the same dilution line.

In this study a microemulsion system comprising Mygliol 812®, Labrasol®, Plurol Oleique® and double distilled water was selected to improve the solubility of a specific cyclooxygenase-2 inhibitor, celecoxib. Celecoxib is a weakly acidic (pKa is 11.1) and hydrophobic (log P is 3.5) drug, almost insoluble in water (3–7 μg ml^{-1}; at pH 7 and 40 °C). The gradual changes in the microstructure of the unloaded and drug-loaded systems on dilution have been investigated by conductivity, viscosity, density and surface tension measurements and the influence of the microstructure on release behaviour of solubilized celecoxib has been evaluated. Additionally the influence of celecoxib on the stability of drug-loaded systems during 3 months storage at 40 °C has been examined.

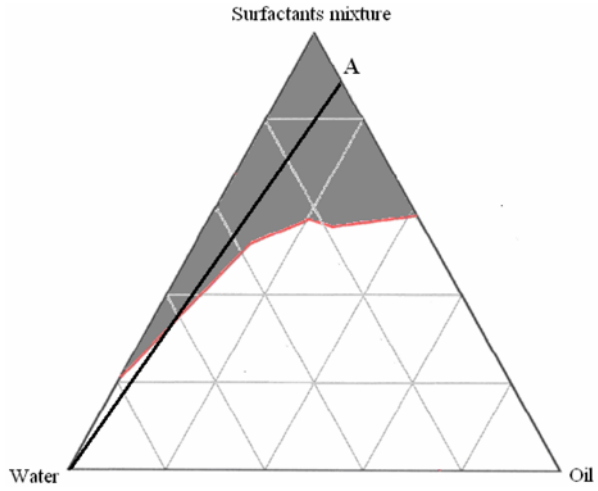

Figure 1. Phase diagram of the system containing Labrasol®/Plurol Oleique®/Miglyol 812®/water. A – the investigated dilution line, dark area – microemulsions, white area – unstable emulsions.

Table 1. Composition of the microemulsion samples along the dilution line (shown in Figure 1).

Sample	Water [%]	Miglyol 812® [%]	Surfactant mixture [%]
1	0.00	12.00	88.00
2	4.76	11.43	83.81
3	11.11	10.67	78.22
4	16.70	10.00	73.30
5	21.60	9.41	68.99
6	27.27	8.73	64.00
7	31.03	8.28	60.69
8	36.51	7.62	55.87
9	41.18	7.06	51.76
10	45.21	6.58	48.21
11	50.00	6.00	44.00
12	55.55	5.34	39.11

2. Experimental

2. 1. Materials

The microemulsion system was composed of the medium chain triglyceride Mygliol 812® (Hüls, Germany) as lipophilic phase, caprylocaproyl macrogolglycerides Labrasol® (Gattefosse, France) as surfactant, polyglyceryl-6 dioleate Plurol Oleique® (Gattefosse, France) as cosurfactant, and double distilled water as hydrophilic phase. The lipophilic drug celecoxib was obtained from Lek Pharmaceuticals d.d.. All chemicals were of laboratory grade.

2. 2. Methods

2. 2. 1. Microemulsion Preparation

A phase diagram (Figure 1) was constructed at room temperature by admixing the appropriate quantities of the various components by gentle hand mixing.[17] A stock solution was prepared comprising 88 wt. % of surfactant mixture and 12 wt. % of Mygliol 812®. The appropriate amount of water was then added to obtain the desired microemulsion composition (Table 1). In order to evaluate their delivery potential, drug-loaded microemulsions were prepared by adding celecoxib to already prepared microemulsions at 1 % concentration.

2. 2. 2. Conductivity Measurements

Electrical conductivity of the samples was measured using a conductivity meter MA 5964 (Iskra, Slovenia) with a home-made conductivity cell with constant of 0.7265 cm^{-1}. Measurements were made in triplicate at 20 ± 0.5 °C.

2. 2. 3. Viscosity Measurements

Viscosity of microemulsions was measured with a Hoeppler's viscometer at 20 ± 0.5 °C. The falling time of

ball was measured three times. The density of the ball was 8.135 g cm^{-3} and the constant 0.12234 mPa cm^3 g^{-1}

2. 2. 4. Surface Tension

Surface tension was measured by Kruss processor tensiometer K21 (Kruss GmbH, Germany) using Wilhelmy's plate method at 20 ± 0.5 °C. A square platinum plate was cleaned, rinsed with bidistilled water and heated in a reductive flame to purge all impurities. This cleaning procedure was repeated before every measurement. All measurements were made in triplicate.

2. 2. 5. Density Measurements

The density of microemulsions and their components was measured with a Density Meter – DMA 5000 (Anton Paar, Austria). Temperature was controlled at 20.00 ± 0.009 °C. The accuracy of density measurements was within ± 5 × 10^{-6} kg dm^{-1}.

2. 2. 6. Solubilization Capacity

The saturated solubility of celecoxib in the selected microemulsions along the dilution line A was determined by adding excess drug and stirring continuously for at least 72 h at 20 ± 0.5 °C to reach equilibrium. After centrifugation (4000 rpm for 30 min) the supernatant was filtered with a 0.45 μm membrane filter (Minisart®-RC, Sartorius, Germany) and analyzed by HPLC after appropriate dilution with a mixture (80:20 v/v) of acetonitrile and bidistilled water.

2. 2. 7. Dissolution Studies

Celecoxib release through a hydrophobic PTFE membrane (pore size: 0.45 μm, Sartorius, Goettingen, Germany), soaked in receptor solution 24 h before experiments, was determined with a Franz diffusion cell with an area of 0.785 cm^2. The cell held 8 ml of receptor medium (stirred magnetically at 150 rpm), and 500 μl of microemulsion on the donor side. To take account of the very low solubility of celecoxib, isopropyl myristate solution with 1.6 wt. % Labrasol® and 0.4 wt. % Plurol Oleique® was used as a suitable receptor phase. The system was kept in a temperature-controlled water bath at 35 ± 0.5 °C and the receptor phase was stirred continuously. At predetermined time intervals (15, 30, 45, 60, 120, 180, 240, 300 and 360 min) 0.3 ml samples were taken and replaced by the same volume of fresh, preheated receptor phase. Each experiment was carried out in triplicate.

The release profiles were evaluated by fitting the experimental data to equations describing different kinetic orders. Linear regression analyses were made for zero-order ($M_t/M_0 = k \cdot t$), first-order ($\ln (M_0 - M_t) = k \cdot t$) and Higuchi ($M_t/M_0 = (k \cdot t)^{1/2}$) kinetics, where M_t/M_o is the celecoxib fraction released at time t and k is the kinetic constant.

2. 2. 8. Stability Studies

Tightly closed glass flasks with celecoxib-loaded microemulsions were stored light protected at 40 ± 0.5 °C for 90 days. At 0, 45 and 90 days they were evaluated for their chemical and physical stability. Chemical stability was expressed in terms of celecoxib content. Physical stability was evaluated by visual inspection for their organoleptic properties, homogeneity and transparency, and by measuring surface tension, electrical conductivity, density and viscosity.

2. 2. 9. Analytical Methods

Celecoxib content was analyzed by HPLC (Agilent 1100). An ODS 250 × 4.6 HPLC column (Thermo, United Kingdom) was maintained at 25 °C during the experiment. Mobile phase, consisting of acetonitrile and water (60:40 v/v), was pumped through the system at a constant flow rate of 1 ml min^{-1}. Celecoxib was detected at 258 nm.

3. Results and Discussion

3. 1. Conductivity Measurements

Electrical conductivity measurements provide structural information, mainly on possible transitions along the dilution lines.[8] Electrical conductivity was measured as a function of weight ratio of aqueous phase Φ (wt. %) for the oil-surfactant/co-surfactant mixture along the dilution line A (shown in Figure 1). It is important to point out that the occurrence of the percolation transition by electrical conductivity measurements for microemulsions with non-ionic surfactants is usually studied in the presence of the dissolved electrolyte.[18] However, the present microemulsion system, containing non-ionic amphiphiles, exhibited electroconductive behaviour in spite of its non-ionic type, as has already been reported.[5] A possible explanation for such behaviour is the natural origin of the surfactants, which is associated with the presence of impurities that contribute to the electroconductance of the systems studied.

The electrical conductivity was ~1.433 μS cm^{-1} for bidistilled water and ~0.005 μS cm^{-1} for Miglyol 812®. The conductivity increases with aqueous phase dilution (Figure 2). The behaviour of microemulsions exhibits the profile characteristic of percolative conductivity.[19] The conductivity profile revealed three different solubilization regions, manifested in three different slopes. In the region with low water content (Φ < 27 wt. %) the conductivity of the selected systems is low, suggesting that the water droplets are isolated and exhibit little interaction, i.e. a w/o microemulsion. In the middle region (27 wt. % < Φ < 45

wt. %) the conductivity increases linearly and sharply (k = 6.3, R = 0.9996). It could be concluded that, beyond the percolation threshold, interactions between the aqueous domains become increasingly important and form a network of conductive channels (bicontinuous microemulsion). With further increase in water content (Φ > 45 wt. %), the slope of the curve decreases (k = 4.7, R = 0.9979), demonstrating the full transformation of the bicontinuous domain into an o/w microemulsion. At Φ > 55 wt. % water, a macroscopic phase was formed. The percolation threshold can be determined from the slope of the plot of dσ/dΦ) as a function of a water weight ratio, Φ (Figure 2 inset). The presence of percolative behaviour in the bicontinuous region was confirmed by the maximum of the first derivative at ~ 33 wt. % of water.[20]

The conductivity of the systems containing 1 wt. % celecoxib was higher than for unloaded microemulsions; however the shape of the curve did not change (Figure 2), which suggests that incorporation of drug did not influence the microstructure of the system. The influence of drug loading is minimal, as expected, when oil is the continuous phase, but becomes more pronounced once the continuous phase is water and the hydrophilic part of the drug molecule faces the water.

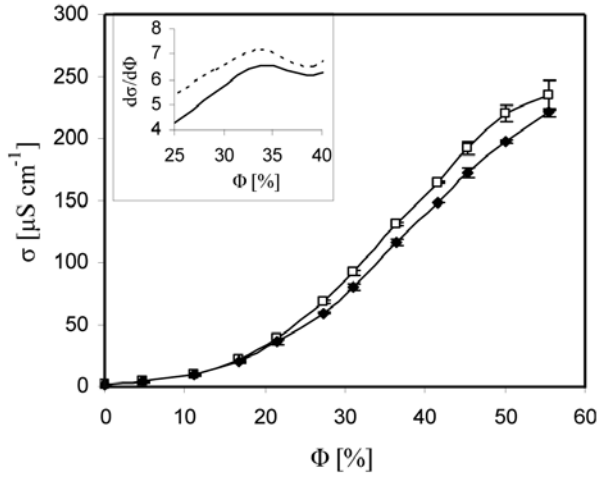

Figure 2. Electrical conductivity (σ) of selected unloaded (-◆-) and drug-loaded (-□-) microemulsions as a function of the water weight ratio (Φ). Inset: the first derivative of the electrical conductivity as a function of the water weight ratio for unloaded (solid line) and drug-loaded (dotted line) systems.

3. 2. Viscosity Measurements

The dependence of dynamic viscosity for the oil, surfactant/co-surfactant mixture along the dilution line A on the water weight fraction is shown in Figure 3. The viscosity increased from 132 to 144 mPa s as Φ increased from 0 to 11 wt. %, which is in agreement with previous findings.[21] A possible explanation for this initial viscosity increase are the attractive interactions and aggregation of water droplets, including molecular reorganisation on the interface. With further increase in Φ up to 55 wt. % the viscosity decreased from 144 to 40 mPa s. However, the decrease was less pronounced when Φ was between 27 and 45 wt. %. This is most probably due to the clustering of the droplets at the percolation threshold, which leads typically to an increase in viscosity and conductivity.[3] It has been found that the percolation threshold can also be determined from the plot of (1/η) (dη/dΦ) versus Φ (Figure 3 inset).[20] The maximum at ~33 wt. % of water coincides well with that of the plot of (dσ/dΦ) versus Φ.

Viscosity depends largely on the microemulsion structure, i.e., the type and shape of aggregates, concentration, and interactions between dispersed droplets. Therefore, it can be used to obtain important information concerning structural transformations in microemulsions, although not necessarily the points at which the transition occurs or is completed.[20] In the present study the inversion point, defined by the viscosity data, coincides well with the transition point determined by electrical conductivity measurements and suggests transformation of the system structure from oil continuous (Φ < 27 wt. %), via bicontinuous (27 wt. % < Φ < 45 wt. %), to water continuous (Φ > 45 wt. %).

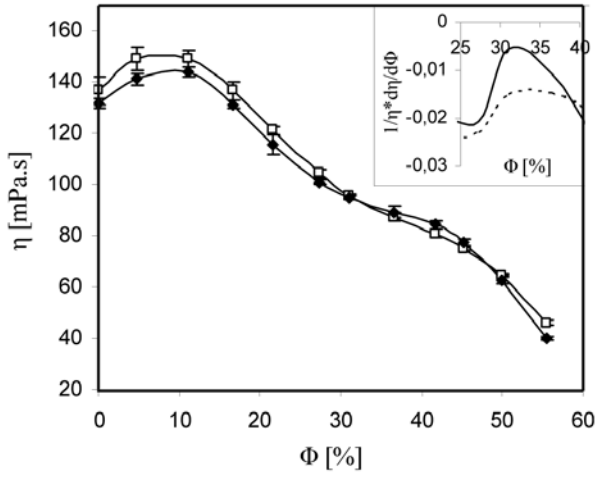

Figure 3. Viscosity (η) of selected unloaded (-◆-) and drug-loaded (-□-) microemulsions as a function of the water ratio (Φ). Inset: plot of (1/η).(dη/dw) as a function of the water weight ratio for unloaded (solid line) and drug-loaded (dotted line) systems.

The general viscosity patterns of unloaded and celecoxib-loaded microemulsions are similar (Figure 3). When celecoxib is partitioned between the hydrophobic tails of the surfactants, or dissolved in continuous oil phase, the viscosity of the celecoxib-loaded systems is slightly higher than that of the unloaded systems. The presence of celecoxib in the bicontinuous region or oil droplets (o/w microemulsions) did not affect the viscosity of the systems.

3. 3. Surface Tension and Density

Values of surface tension and density are plotted against water weight ratio (Figures 4 and 5). The surface tension decreased with increase in Φ. The decrease is linear between 5 to 27 wt. % of water (k = –0.08, R = 0.9999). and above 41 wt. % of water (k = –0.03, R = 0.9999). In the middle area (27 wt. % < Φ < 41 wt. %) an inflection point occurs, as seen also from the first derivatives (Figure 4 inset). This suggests that structural changes are taking place in this region. Incorporation of celecoxib at 1 wt % concentration did not influence the surface tension measurements.

In the density curves, breaking points of the lines at similar water weight ratios are observed. The densities of unloaded and celecoxib-loaded systems increased monotonically up to ~11 wt. % of water, after that remaining constant or decreasing slightly up to 27 wt. % of water. With further increase in water content (Φ > 27 wt. %) the density of the formulations decreased linearly on the whole area, however the slope of the curve changed from –0.0005 (R = 0.9999) to –0.0007 (R = 0.9999) at ~45 wt. % of water.

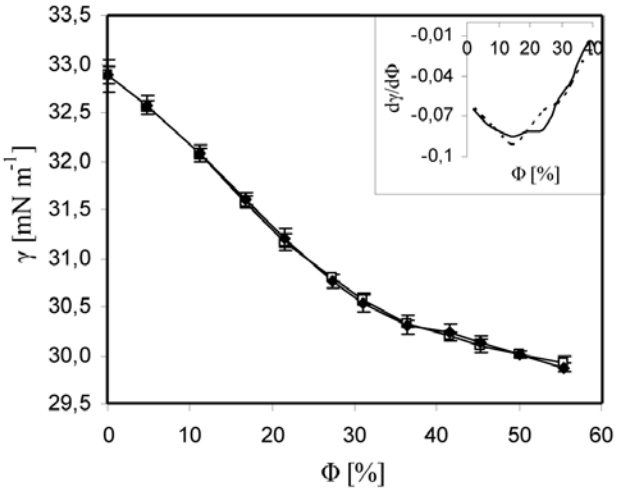

Figure 4. Surface tension (γ) of selected unloaded (-◆-) and drug-loaded (-□-) microemulsions as a function of the water ratio (Φ). Inset: the first derivative of the surface tension of unloaded (solid line) and drug-loaded (dotted line) systems as a function of the water weight ratio.

The volume of the microemulsions was calculated from the measured density and the excess volume, $V^E = V_{exp.} - V_{id.}$, obtained as a function of the water content (Figure 5 inset). Ideal additivity of the components' volumes was assumed: water, Miglyol 812® and surfactant mixture, with densities 0.997817, 0.945401 and 1.058079 g.cm^{-3} respectively. The volumes are in fact seen not to be additive. It is evident that a contraction of volume occurs for all samples, and real volume is therefore lower than the ideal volume. Considerable contraction of volume occurs up to ~21 wt. % of water. Between 27 and 41 wt. % of water the volumes are very similar, suggesting that attractive interactions are similar in this region. With further increase in water content (Φ > 41 wt. %), V^E increased again, indicating that the attractive interactions are declining, which results in a smaller contraction of volume.

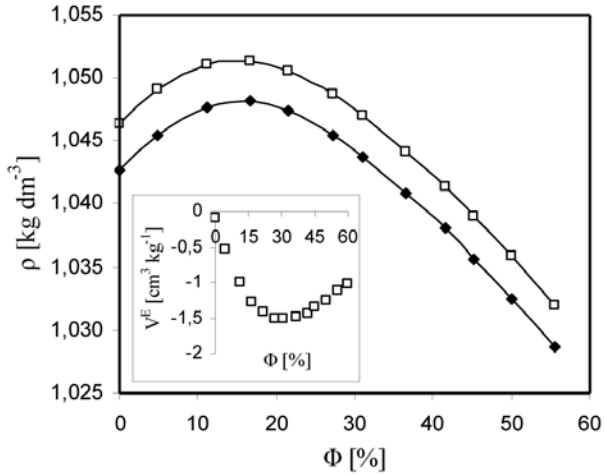

Figure 5. The variation of density (ρ) of selected unloaded (-◆-) and drug-loaded (-□-) microemulsions as a function of water weight ratio (Φ). Inset: The excess volume, V^E, of the water-Labrasol®/Plurol Oleique®-Miglyol 812® microemulsions as a function of the water weight ratio.

3. 4. Solubilization Capacity

The unique solubilization properties of microemulsions have drawn attention for their use as vehicles for drug delivery. We tested the correlation between microemulsion composition and microstructure upon dilution and maximum solubilization capacity. The maximum solubilization of celecoxib (~280 mg ml^{-1}) was achieved in the surfactant-oil mixture (Figure 6), due to the presence of reverse micelles. On dilution with aqueous phase, solubilization capacity decreased until it reached a value of approximately 20 mg ml^{-1} at 60 wt. % of aqueous phase. The reduction in the solubilization capacity may reflect decrease in the oil/surfactant mixture content as well as structural changes that occur on dilution.[13]

The solubilization profile (Figure 6) reveals three regions. In the first, up to 10–20 wt. % aqueous phase (w/o microemulsion), a very large decrease in solubilization capacity was observed. In the second region (20 wt. % < Φ < 45 wt. %) the w/o droplets are transformed into bicontinuous domains, resulting in a moderate decrease in the solubilization capacity. With further dilution to 50–60 wt. % aqueous phase, the system inverts to o/w droplets. At high water content, the total amount of oil, and also surfactants, is low, which results in lower and almost unchanged solubilization capacity. It has been reported that o/w type of interface can be loaded only with difficulty with a hydrophobic drug. The interface is less tolerant to

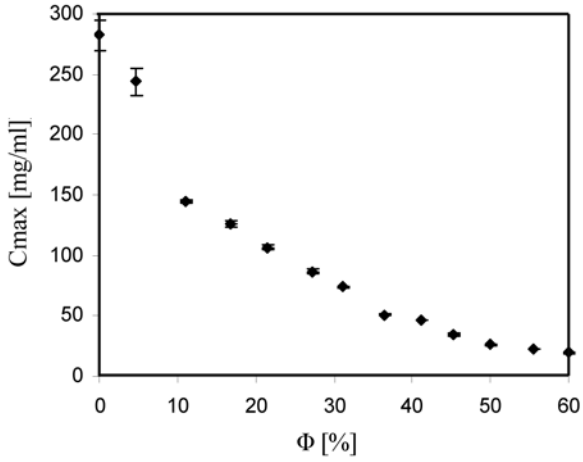

Figure 6: Celecoxib solubilization capacity in microemulsion systems along dilution line A as a function of the water weight ratio (Φ).

the drug guest molecule, since the surfactant in the o/w droplets is tightly packed around the oil droplets, leaving less free space for celecoxib incorporation within the hydrophobic tails of surfactant molecules.[13]

3. 5. Drug Release

In vitro release studies with an artificial hydrophobic membrane can provide information about the diffusion of a drug, which depends on the physico-chemical properties of components, vehicle internal structure, and interaction between drug and vehicle.[20,22,23] On the basis of microstructure analysis, five samples, whose composition is shown in Table 1, were selected for the in vitro drug release study. Sample 4 is of w/o type, 6 represents the start of the percolation phenomenon, 9 is bicontinuous phase, 10 is located in the border area between bicontinuous and water continuous phase, and 12 is the water continuous system. The release profiles of tested ME samples are shown in Figure 7a. Celecoxib release through artificial membrane was characterized by two parameters: the amount released after 6 hours and the rate of drug release (Figure 7b). The kinetics of release was also calculated. Zero, first order and Higuchi kinetics were tested for each formulation. The calculated Pearson's coefficients (in the range of 0.9916–0.9985) indicate the best fit for zero order kinetics.

The amount and rate of celecoxib release differ between microemulsion carriers with different internal microstructure, however the difference is significant only for samples 4 and 12. Comparing the amounts of released celecoxib after 6 hours as well as the release rate (Figure 7b) the slowest release was observed for sample 4 (drug release rate: 2.48% h^{-1}); both parameters increase with increasing amounts of water in the delivery system. All samples with bicontinuous structure (samples 6, 9 and 10) yield approximately the same profiles (drug release rate: 3.06–3.17% h^{-1}) indicating that drug release is not dependent on the degree of percolation. Podlogar et al. also observed similar behaviour.[22] The fastest release profile was identified for sample 12 (drug release rate: 3.64% h^{-1}). This is in contrast to our expectations that drug release from o/w microemulsion, in which celecoxib is predominantly located in the oil droplets, will be hampered by the external hydrophilic phase. A possible explanation could be that, in addition to the internal microstructure, the solubilization capacity greatly influences the drug release from microemulsions. For the microemulsion studied, the celecoxib solubilization capacity is decreased from ~126 mg ml^{-1} (sample 4) to ~23 mg ml^{-1} (sample 12) with increase in water content from 16.7 (sample 4) to 55.55 wt. % (sample 12).

Evidently, the release behaviour of celecoxib is influenced by the carrier microstructure as well as by its solubilization capacity, and can be predicted to a certain ex-

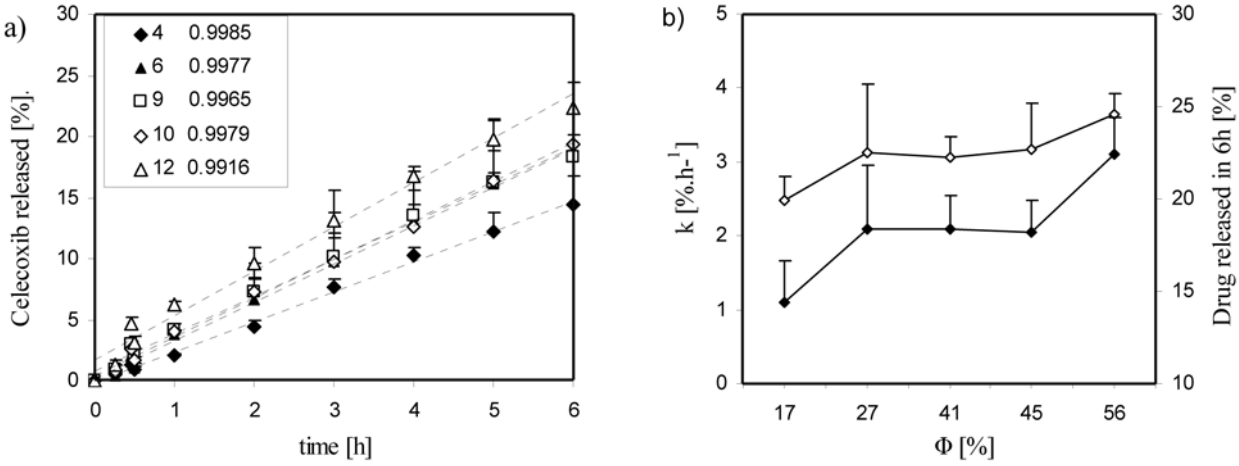

Figure 7: a) Release profiles of celecoxib from representative samples 4 (-◆-), 6 (-▲-), 9 (-□-), 10 (-◇-) and 12 (-△-), of compositions given in Table 1. Lines: zero order release kinetics, Pearson's coefficients are given next to the symbols in the legend. b) Correlation between release parameters; (-○-) celecoxib release rate and (-●-) % of released celecoxib after 6 hours as function of the water weight ratio in the microemulsion.

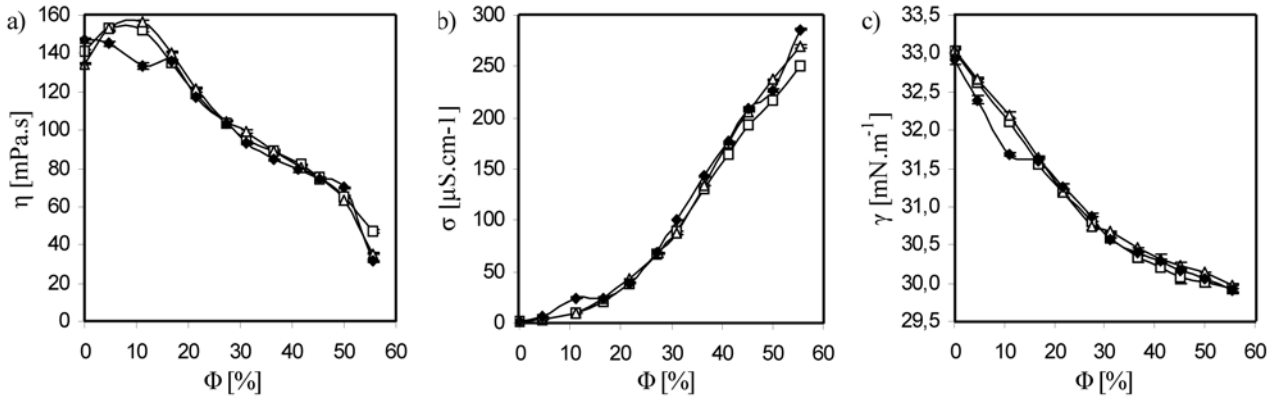

Figure 8: a) Dynamic viscosity (γ), b) electrical conductivity (σ), and c) Surface tension (γ) of drug-loaded microemulsions as a function of the water weight ratio (Φ) after 0 (-□-), 45 (-△-) and 90 (-◆-) days storage at 40 °C.

tent, using a combination of several tested methods for physical characterization of microemulsions.

3. 6. Stability Studies

After 90 days storage at 40 °C, all samples remained transparent and no precipitation or phase separation was observed. However, a slight darkening of their macroscopic appearance was noted, probably due to temperature-induced oxidation of Plurol Oleique®. Microemulsion stability is routinely evaluated by visual inspection; however, their macroscopic appearance does not provide any information regarding the stability of their internal microstructure. Therefore viscosity, conductivity and surface tension were also monitored during stability testing. The measurements confirmed that microemulsions suffered no appreciable structure changes during the first 45 days, although some differences in viscosity (Figure 8a), conductivity (Figure 8b) and surface tension (Figure 8c) could be observed at certain compositions after 90 days storage, indicating microstructure changes. Systems consisting of 17 to 45 wt. % water (bicontinuous structure) did not suffer any considerable changes and their internal structure remained stable throughout.

We also evaluated the chemical stability of celecoxib in the tested formulation, defined as the retention of at least 90 % of the initial concentration. It was found acceptable when water phase content was kept below 55 wt. % (data not shown).

4. Conclusions

A combination of conductivity, viscosity, density and surface tension measurements was used to study the structural properties of the quaternary microemulsion system Mygliol 812®/Labrasol®/Plurol Oleique®/water and of its celecoxib-loaded system. The percolation phenomenon confirmed by conductivity and viscosity measurements are convincing evidence that the system undergoes a structural inversion from oil-continuous to water-continuous over bicontinuous structure on the selected dilution line. We may conclude that a microemulsion containing less than ~ 27 wt. % of water is oil continuous, between 27 and 45 wt. % of water is water as well as oil continuous, i.e. bicontinuous, and finally, at more than 45 wt. % of water is of o/w type. On incorporation of celecoxib at 1 wt. % concentration, the microemulsions remain stable and optically clear, with no phase separation or considerable microstructure changes. We have shown that a combination of tested methods for physical characterization of microemulsions can also be used to predict the celecoxib release behaviour. We found that the latter is influenced by the microstructure as well as solubilization capacity of the system. Stability testing of celecoxib-loaded microemulsions revealed that they are stable over 90 days storage at 40 °C. On the basis of our results we can conclude that this quaternary microemulsion system is suitable for improving the solubility of similar poorly water-soluble drugs.

5. Acknowledgements

The authors would like to express their gratitude to Gattefosse, S. A. for kindly supplying the surfactants used in this study. The work was partially supported by COST Action D43.

6. References

1. S. Tenjarla, *Crit. Rev. Ther. Drug Carrier Syst*. **1999**, *16*, 461–521.
2. R. P. Bagwe, J. R. Kanicky, B. J. Palla et al, *Crit. Rev. Ther. Drug Carrier Syst.* **2001**, *18*, 77–140.
3. I. Amar, A. Aserin, N. Garti, *Coll. Surf. B: Biointerfaces*, **2004**, *33*: 143–150.
4. F. Poglogar, M. Gašperlin, M. Tomšič, A. Jamnik, M. Bešter Rogač, *Int. J. Pharm*. **2004**, *276*, 115–128.

5. L. Djordjevic, M. Primorac, M. Stupar and D. Krajišnik, *Int. J. Pharm.* **2004**, *271*, 11–19.
6. M. Fanun, *J. Mol. Liquids* **2008**, *139*, 14–22.7.
7. S. K. Mehta, G. Kaur and K. K. Bhasin, *Pharm. Res.* **2008**, *25*, 227–236.
8. M. Malmsten, In: P. Kumar, K. L. Mittal (Ed.): Handbook of Microemulsion Science and Technology, Marcel Dekker, New York, **1999**.
9. P. Boonme, K. Krauel, A. Graf, T. Rades and V. B. Junyaprasert, *AAPS Pharm Sci Tech.* **2006**, *7*, Article 45.
10. M. Gradzielski, *Curr. Opin. Colloid Interface Sci*. **2008**, *13*, 263–269.
11. Y. Xie, R. Ye and H. Liua, *Coll. Surf. Physicochem. Eng. Aspects.* **2007**, *292*, 189–195.
12. P.P. Constantinides, *Pharm. Res.* **1995**, *12*, 1561–1572.
13. N. Garti, M. Avrahami, A. Aserin, *J. Colloid Interface Sci.* **2006**, *299,* 352–365.
14. A. Spernath, A. Aserin, *Adv. Colloid. Interface. Sci*. **2006**, *128–130*, 47–64.
15. J. L. Salager, R. E. Antün, D. A. Sabatini, J. H. Harwell, E. J. Acosta, L. I. Tolosa, *J Surfactants Detergents* **2005**, *8*, 3–21.
16. N. Sadurnía, C. Solans, N. Azemara M. J. García–Celma. *Eur. J. Pharm. Sci.* **2005**, *26*, 438–445.
17. M. Gašperlin and P. Špiclin, *Sci. Pharm.* **2001**, *69*, 157–158.
18. S. Weigert, H. F. Eicke and W. Meier, *Physica A* **1997**, *242*, 95–103.
19. G. S. Grest, I. Webman, S. A. Safran, A. L. R. Bug, *Phys. Rev. A*. **1986**, *33*, 2842–2845.
20. M. Gradzielski H. Hoffmann, In: P. Kumar, K. L. Mittal (Ed.): Handbook of Microemulsion Science and Technology, Marcel Dekker, New York, **1999**, p: 375.
21. K. E. Bennett, J. C. Hatfield, H. T. Davis, C. W. Macosko and L. E. Scriven, In: I. D. Robb (Ed.): Microemulsions. Plenum Press, New York, **1982**, p: 65–84.
22. F. Podlogar, M.Bešter Rogač and M. Gašperlin, *Int. J. Pharm.* **2005**, *302*, 68–77.
23. L. Djordjevic, M. Primorac and M. Stupar, *Int. J. Pharm*. **2005**, *296*, 73–79.

Povzetek

Proučevali smo spremembo notranje strukture mikroemulzij, ki nastanejo po razredčevanju začetne zmesi sestavljene iz 12 % (m/m) Mygliola 812® in 88 % (m/m) emulgatorja (Labrasol®) ter koemulgatorja (Plurol Oleique®) v razmerju 4:1. Rezultati meritev električne prevodnosti, viskoznosti, površinske napetosti ter gostote nakazujejo, da vzdolž preučevane razredčitvene premice potekata dva strukturna prehoda; pri ~27 % (m/m) vode mikroemulzija s kontinuirano oljno fazo (v/o) najprej preide v bikontinuiran sistem, nakar sledi prehod slednjega v mikroemulzijo s kontinuirano vodno fazo (o/v) pri ~45 % (m/m) vode. Vgradnja 1 % (m/m) celekoksiba ni vplivala na stabilnost in mikrostrukturo nastalega sistema. Proučevali smo tudi hitrost in obseg sproščanja celekoksiba iz posameznih mikroemulzijskih struktur ter ugotovili, da je sproščanje odvisno tako od mikrostrukture kot od solubilizacijske kapacitete sistema in ga je v določeni meri mogoče napovedati. Potrdili smo tudi stabilnost mikroemulzij s celekoksibom med 90 dnevnim shranjevanjem pri 40 °C.