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In vitro release of diclofenac diethylamine from caprylocaproyl macrogolglycerides based microemulsions

Ljiljana Djordjevic*, Marija Primorac, Mirjana Stupar

Department of Pharmaceutical Technology and Cosmetology, Faculty of Pharmacy, Vojvode Stepe 450, P.O. Box 146, 11221 Belgrade, Serbia and Montenegro

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Abstract

The purpose of the present study was to determine the influence of both formulation parameters and vehicle structure on in vitro release rate of amphiphilic drug diclofenac diethylamine (DDA) from microemulsion vehicles containing PEG-8 caprylic/capric glycerides (surfactant), polyglyceryl-6 dioleate (cosurfactant), isopropyl myristate and water. From the constructed pseudo-ternary phase diagram at surfactant–cosurfactant mass ratio (K_m 1:1), the optimum oil-to-surfactant–cosurfactant mass ratio values (O/SC 0.67–1.64) for formulation of microemulsions with similar concentrations of hydrophilic, lipophilic and amphiphilic phases (balanced microemulsions) were found. The results of characterization experiments indicated bicontinuous or nonspherical water-continuous internal structure of the selected microemulsion vehicles. Low water/isopropyl myristate apparent partition coefficient for DDA as well as elevated electrical conductivity and apparent viscosity values for the investigated microemulsion formulations containing 1.16% (w/w) of DDA, suggested that the drug molecules was predominantly partitioned in the water phase and most likely selfaggregate and interact with interfacial film. Release of DDA from the selected water-continuous (W/O), oil-continuous (O/W) and balanced microemulsions was investigated using rotating paddle dissolution apparatus modified by addition of enhancer cell. A linear diffusion of DDA through regenerated cellulose membrane was observed for the W/O and O/W formulations with the low content of dispersed phase. Non-linearity of the drug release profile in the case of bicontinuous formulations was related to the more complex distribution of DDA including interactions between the drug and vehicle. The membrane flux value increases from 25.02 $\mu g\,cm^{-2}\,h^{-1}$ (W/O microemulsion) to 117.94 $\mu g\,cm^{-2}\,h^{-1}$ (O/W microemulsion) as the water phase concentration increases. Moreover, the obtained flux values for balanced microemulsions (29.38–63.70 $\mu g\,cm^{-2}\,h^{-1}$) suggested that bicontinuous microstructure hampers the release of the amphiphilic drug.

Keywords: Microemulsion; Caprylocaproyl macrogolglycerides; Release rate; Diclofenac diethylamine

* Corresponding author. Tel.: +381 11 397 0379; fax: +381 11 397 2840.
E-mail address: girasole@ptt.yu (L. Djordjevic).

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1. Introduction

During the recent decades various colloidal systems have been investigated as suitable pharmaceutical vehicles for successful dermal and transdermal delivery of active substance. Microemulsion systems, owing to their thermodynamic stability, ease of preparation, transparency, low viscosity, and considerable potential for solubilising variety of drugs, often have been the object of investigations in relation to drug delivery (Kumar and Mital, 1999). The results of numerous studies (Bonina et al., 1995; Schmalfuß et al., 1997; Delgado-Charro et al., 1997; Trotta et al., 1997; Bolzinger et al., 1998; Kreilgaard et al., 2000, 2001; Baroli et al., 2000; Lehmann et al., 2001; Spiclin et al., 2003) have suggested that microemulsion vehicles have a significant potential to increase penetration of hydrophilic, lipophilic, and amphiphilic substances into and through the skin compared to conventional vehicles. Depending on physico-chemical properties of components, microemulsion internal structure (usually water in oil (W/O), oil in water (O/W) or bicontinuous), and interactions between drug and vehicle, these microemulsions display a rich behaviour regarding the release of solubilized material (Kumar and Mital, 1999). Also, the results of several transdermal drug delivery studies have suggested that microemulsions with similar amount of water, oil and tensides (so called balanced microemulsions) have the most favourable properties as skin penetration enhancers (Delgado-Charro et al., 1997; Bolzinger et al., 1998). Anyhow, still there are no general conclusions about correlation between composition, structure and drug delivery potential of the system. The addition of active substance in the pharmaceutical microemulsions may affect significantly the stability and structure of the system (Kumar and Mital, 1999). Also, the incorporated drug participates in the microstructure of the system and may influenced it, especially if the drug posesses amphiphilic and/or mesogenic properties and such interactions may strongly influence drug release (Müeller-Goymann et al., 1995; Kriwet and Müeller-Goymann, 1995). Diclofenac diethylamine (DDA) (Fig. 1) is a nonsteroidal anti-inflammatory drug which have been used for dermal application more often than other diclofenac salts, due to its amphiphilic nature. It has been observed that DDA molecules form micelles and lyotropic liquid crystals in water (Kriwet and Müeller-Goymann, 1993). Furthermore, the interactions of this drug with phospholipids have been reported (Engehausen and Müeller-Goymann, 1992), and the fluidizing effect of DDA on the human stratum corneum lipids has been detected (Kriwet and Müeller-Goymann, 1995). The main goal of the present paper was to investigate both the influence of DDA on physico-chemical properties of a microemulsion vehicle and the correlation between structure and composition of the vehicle and in vitro drug release.

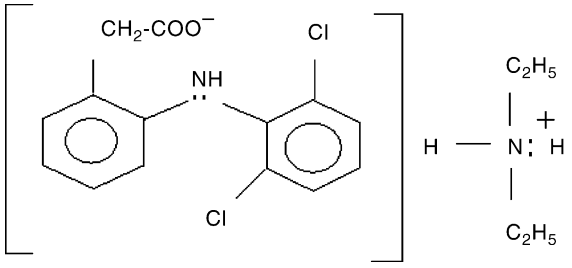

Fig. 1. Structural formula of diclofenac diethylamine.

The important disadvantage of the microemulsion vehicles is that the microemulsion state usually forms within specific concentration ranges of components and often requires a high content of surfactants inducing significant alterations to the skin barrier function (Kumar and Mital, 1999; Lawrence and Rees, 2000). 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). There have been several studies involving microemulsion drug delivery vehicles for topical application based on low-irritant caprylocaproyl macrogolglycerides as surfactant, and polyglycerol fatty acid esters as cosurfactant (Gašperlin and Špiclin, 2001; Delgado-Charro et al., 1997; Kreilgaard et al., 2001; Djordjevic et al., 2004). However, there were no attempts to establish a surfactant–cosurfactant mass ratio (K_m) that is adequate for formulation of microemulsions containing relatively high and similar percentages of both water and oil phases. Thus, the second goal of this study was to optimise the mass ratios between the surfactant (PEG-8 caprylic/capric glycerides), cosurfactant (polyglyceryl-6 dioleate) and oil (isopropyl myristate) in order to formulate balanced microemulsions.

2. Materials and methods

2.1. Materials

PEG-8 caprylic/capric glycerides (Labrasol®) and polyglyceryl-6 dioleate (PlurolOleique®) 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, Serbia and Montenegro). 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 phase, at room temperature (Gattefossé, 1994). Labrasol®, the surfactant (S), and PlurolOleique®, 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 K_m 1:1 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 to each oily mixture. During the titration, samples were stirred to allow equilibration. Following addition of aliquot of water the mixture was visually examined for transparency. Transparent, single-phase mixtures were designated as microemulsions.

2.2.2. Selection of microemulsion formulations for detailed studies

For further studies, from the constructed pseudo-ternary phase diagram, three potential microemulsion vehicles (referred to as G, H, and I in Table 1 and Fig. 1) at O/SC 1.64, 1.34, and 1.00, respectively, were selected and prepared. In the drug release experiments, beside the balanced microemulsions G–I, were included highly diluted water-in-oil microemulsion (referred to as A in Table 1) and oil-in-water microemulsion (referred to as F in Table 1) which were chosen from the pre-constructed pseudo-ternary phase diagram and characterization study of the same quaternary system (Djordjevic et al., 2004). The microemulsion vehicles were formed spontaneously at room temperature by admixing appropriate quantities of Labrasol®, PlurolOleique®, isopropyl myristate, and water. Additionally, DDA was dissolved into preweight vehicles at a concentration ratio of 1.16 % (w/w). Both, unloaded and drug-loaded microemulsions were prepared 48 h before investigations, and stored at room temperature.

2.3. Microemulsion characterization

2.3.1. Polarized light microscopy

Unloaded and drug-loaded vehicles were examined by polarized light microscopy (Aus Jena polarizing microscope, Carl Zeiss, Oberkochen, Germany) in order to distinguish isotropic microemulsions from anisotropic lamellar and hexagonal mesophases.

2.3.2. Centrifugation

Physical stability of the selected vehicles as well as drug-loaded microemulsions were tested applying centrifugation (Sigma 2–16 centrifuge, Sigma Laborzentrifugen GmbH, Osterode, Germany) at 13 000 rpm for 30 min.

2.3.3. Conductivity measurements

Electrical conductivity (σ) of formulated samples was measured using a conductometer CDM 230 (Radiometer, Copenhagen, Denmark), at $20 \pm 2\,^{\circ}C$ and the frequency of 94 Hz. Experiments were carried out in

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

	G	H	I	A	F
Water	25.00	32.50	35.00	10.00	60.00
Isopropyl myristate	46.55	38.70	32.50	18.00	8.00
Labrasol®/PlurolOleique® (K_m 1:1)	28.45	28.80	32.50	–	–
Labrasol®/PlurolOleique® (K_m 4:1)	–	–	–	72.00	32.00

triplicate for each sample, and results are presented as average ± S.D.

2.3.4. Rheological measurements

Rheological behaviour of 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 (η') data at shear rate 200 s^{-1} were obtained at 20 ± 1 °C. Experiments were carried out in triplicate for each sample, and results are 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 ± 1 °C.

2.3.6. Apparent partition coefficient

The drug partition coefficient (K_p) at 20 ± 1 °C was calculated according to the concentration of DDA remained in water phase of water/isopropyl myristate systems after 72 h. DDA concentration was determined spectrophotometrically at 275.1 nm (Spectrophotometer Carry 50, Varian, Germany).

2.3.7. In vitro drug release studies

Dissolution profiles of the microemulsion formulations were determined using a rotating paddle apparatus (Erweka DT70, Hausenstamm, Germany), modified by addition of dissolution cell. Dissolution cell (enhancer cell) (VanKel Industries Inc., Edison, USA) was filled with the microemulsion (2 g) and covered with a regenerated cellulose membrane (Cuprophan®, Akzo, Wuppertal, Germany). The cell was capped and placed in the dissolution vessel containing the receptor medium (pH 7.4 phosphate buffer). The receptor medium was maintained at a constant temperature of 32 °C. The rotating paddle speed was 100 rpm. At fixed time intervals (30, 60, 120, 180, 240, 300, 360, 420, and 480 min), samples of 4 ml were withdrawn from the receptor compartment and were immediately replaced by fresh buffer solution. Sink conditions were maintained at all times. All samples were filtered using 0.45 μm MF-Millipore® membrane filter (Millipore Corporation, Bedford, USA) and assayed for DDA. DDA concentration was determined spectrophotometrically at 275.1 nm (Spectrophotometer Cary 50, Varian, Darmstadt, Germany). The dissolution experiments were carried out in triplicate, and data were expressed as mean value ± S.D.

3. Results and discussion

3.1. Phase behaviour

The previous investigation of phase behaviour of water/Labrasol®/Plurol Oleique®/isopropyl myristate system at K_m 4:1 has establish a maximum water solubilisation at O/SC ratios less than 0.250 including a continuous transition from oil- to water-continuous microemulsions (Djordjevic et al., 2004). Thus, the relatively high K_m value was adequate only to formulate microemulsions with low content of oil phase. As the aim of the present phase behaviour investigations was to optimise K_m and O/SC values in order to formulate balanced microemulsions, the concentration of PlurolOleique® was increased so that the surfactant–cosurfactant mass ratio was 1:1, and the obtained results are shown in Fig. 2. Within the dark grey area in the phase diagram are presented numerous

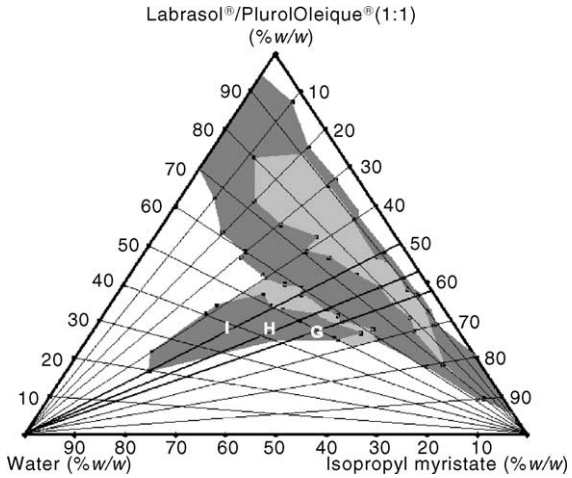

Fig. 2. Pseudo-ternary phase diagram of water/PEG-8 caprylic/capric glycerides/polyglyceryl-6 dioleate/isopropyl myristate system at K_m 1:1, and compositions of the investigated microemulsion vehicles (G–I). The dark grey area represents the transparent mixtures and the light grey area belongs to the opalescent and turbide states of the investigated system at room temperature.

transparent, low-viscous mixtures containing various percentages of constituents. The maximum solubilization of water and oil phases was achieved in the oil–surfactant–cosurfactant mixtures at O/SC values in a range of 1.64–0.67. These data suggest that the lowering K_m from 4:1 to 1:1 the solubilization capacity for oil phase in the investigated system significantly increase. Furthermore, as the O/SC value has been decreased within interval 1.64–0.67, the water phase solubilization capacity has been increased. With the equilibration of the oil and amphiphiles content (O/SC ∼ 1.00) the oil–surfactant–cosurfactant mixture was able to solubilize the maximum amount of water phase (roughly 60%, w/w) at the minimum percentage of surfactant–cosurfactant mixture (roughly 20%, w/w). Most likely, polyglyceryl-6 dioleate enables the formation of more flexible surfactant–cosurfactant interfacial film, which determines the existence of nonspherical aggregates or bicontinuous structures. Also, the higher flexibility of amphiphiles film allows the penetration and association of isopropyl myristate molecules enabling the formation of systems with high capacities for both oil and water phases, and therefore broaden the microemulsion region. The obtained results pointed out the important role of both the cosurfactant and the oil phase for the internal structure of a microemulsion vehicle. Furthermore, from the above investigations, three potential balanced microemulsion vehicles (G–I) were selected (Fig. 1), different from each other by water phase content and O/SC values (Table 1).

3.2. Physico-chemical characterization

The unloaded microemulsion vehicles were isotropic, transparent dispersions and after centrifugation no phase separation could be observed. Due to dynamic nature and small size of surfactant aggregates (typically less than 100 nm) direct examination of microemulsion structure is difficult, and indirect measurement techniques, such as electrical conductivity and rheological studies, can be employed to obtain basic informations about the internal structure (Kahlweit et al., 1987; Strey, 1996). Conductivity values of the investigated balanced microemulsions ranged from 25.7 to 51.5 μS/cm (Table 2). These values have indicated presence of electroconductive channels. Also, latter results were consistent with the previous characterization study and conductivity characteristics of the bicontinuous microemulsions (Djordjevic et al., 2004). The apparent viscosity values of the microemulsion vehicles were generally low and correlation coefficients were the highest for Newtonian flow behaviour (Table 3). The addition of DDA did not have any influence on microemulsions stability and optical texture. The influence of the active ingredient on conductivity and rheological behaviour of microemulsion vehicles is presented in Tables 2 and 3, respectively. DDA strongly affected σ (Table 2). The presence of DDA did not change the flow behaviour, while η' of vehicles was significantly increased in comparison to η' of microemulsions without a drug (Table 3). In general, the values of the isopropyl myristate–water partition coefficient for DDA were very low (Table 2), and it was observed that as the water content in the vehicle increases and the oil content decreases, the drug partitions predominantly in the water phase. Microemulsion vehicles pH value varied from 7.48 to 7.57, and the incorporated drug did not affect significantly pH value of the vehicles (Table 2). Furthermore, due to low pK_a value of DDA (pK_a 4.87) (Ledvige and Corrigan, 1998), at this range of pH values, it was expected a significant generation of diethylamonnium cation, contributing the elevated conductivity of the investigated microemulsions (Table 2). Also, taking the obtained results of drug partition in isopropyl myristate–water system as well as low critical assosiation concentration of DDA

Table 2
Electrical conductivity (σ), pH, and apparent partition coefficient (K_p) of the investigated microemulsions

	Unloaded microemulsions		Drug-loaded microemulsions		K_p
	σ (μS/cm)	pH	σ (μS/cm)	pH	
G	25.7 ± 0.38	7.57	397.0 ± 6.81	7.70	0.329
H	26.4 ± 0.94	7.54	519.0 ± 5.08	7.65	0.112
I	51.5 ± 1.82	7.48	632.0 ± 1.33	7.55	0.082

Table 3
Apparent viscosity (η'), and correlation coefficients (R_{xy}) for the Newtonian flow behaviour of investigated microemulsions

	Unloaded microemulsions		Drug-loaded microemulsions	
	η' (mPa s)	R_{xy}	η' (mPa s)	R_{xy}
G	58.2 ± 0.0013	0.95337	263.0 ± 0.0003	0.99484
H	71.9 ± 0.0002	0.93355	351.0 ± 0.0013	0.99454
I	199.0 ± 0.0005	0.91950	423.0 ± 0.0009	0.99539

(20 mM, 20 °C) (Kriwet and Müeller-Goymann, 1993), it was expected that the microstructure of the investigated vehicles G–I represents the suitable environment for selfaggregation of DDA molecules and possible interactions with the interfacial film. Significant increase of microemulsions apparent viscosity values (Table 3) have confirmed this assumption.

3.3. In vitro drug release

The concentration of DDA in the receiver during the release experiment divided by a membrane surface available for diffusion (4.906 cm^2) is presented in Fig. 3. It is of interest to note that in spite of increasing number of the studies investigating drug release from microemulsions, there were only a few attempts to establish an appropriate mathematical model describing drug release kinetics (Grassi et al., 2000; Sirotti et al., 2002). Starting from the assumptions that there was no influence of the synthetic membrane on the drug permeation, it was expected a linear diffusion of drug molecules from the donor to the receiver compartment. The linear release profile of DDA was observed for the droplet type formulations (A and F) (Fig. 3). Interestingly, drug concentration profile for microemulsions G–I was non-linear. The non-linear trend could be attributable to the more complex distribution of DDA between water, oil and amphiphile phases including stronger drug–vehicle interactions. The values of flux of DDA through the regenerated cellulose membrane from the investigated microemulsions were: 25.02 $\mu g\,cm^{-2}\,h^{-1}$ (A), 117.94 $\mu g\,cm^{-2}\,h^{-1}$ (F), 29.38 $\mu g\,cm^{-2}\,h^{-1}$ (G), 33.21 $\mu g\,cm^{-2}\,h^{-1}$ (H), and 63.70 $\mu g\,cm^{-2}\,h^{-1}$ (I). Most likely, the release of DDA from formulation A, in which the drug is predominantly located in the water droplets, was hampered by the external hydrophobic phase. In the case of bicontinuous and nonspherical water-continuous microemulsions (G–I) the release process was more complex. In general, experimental data suggests that nonspherical microstructure slightly hampers the amphiphilic drug release, probably due to drug/vehicle interactions. Also, the obtained results indicate strong correlation between the water phase concentration and the flux of DDA through the synthetic membrane. The flux value was increased proportionally to the content of water phase, and the maximum of DDA flux was obtained from microemulsion containing the highest percentage of water (formulation F). This observation was well consistent with the previously detected higher DDA diffusion coefficient from the lotion (contains a huge amount of water phase) compared to the lipogel and the mixed micelle gel (Parsaee et al., 2002). This study indicates that the release rate of DDA from the investigated systems depends significantly on both the drug/vehicle interactions and the water volume fraction. However, because of generality of latter observations, it is important to emphasise that the complete informations of drug

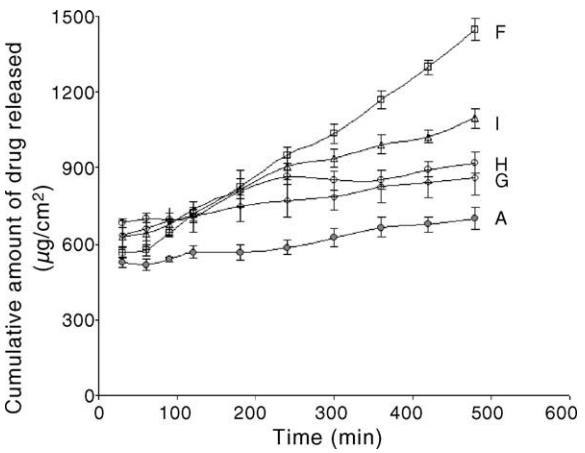

Fig. 3. Dissolution profile of DDA from the investigated microemulsion vehicles containing various concentrations of water: 10.00% (A), 25.00% (G), 32.50% (H), 35.00% (I), and 60% (F).

delivery potential of balanced PEG-8 caprylic/capric glycerides/polyglyceryl-6 dioleate based microemulsions still remain a subject of further, more detailed investigations.

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References

Baroli, B., Lopez-Quintela, M.A., Delgado-Charro, M.B., Fadda, A.M., Blanco-Mendez, J., 2000. Microemulsions for topical delivery of 8-methoxalen. J. Control. Release 69, 209–218.

Bolzinger, M.A., Carduner, T.C., Poelman, M.C., 1998. Bicontinuous sucrose ester microemulsion: a new vehicle for topical delivery of niflumic acid. Int. J. Pharm. 176, 39–45.

Bonina, F.P., Montenegro, L., Scrofani, N., Esposito, E., Cortesi, R., Menegatti, C., Nastruzzi, C., 1995. Effects of phospholipid based formulations on in vitro and in vivo percutaneous absorption of methyl nicotinate. J. Control. Release 34, 53–63.

Delgado-Charro, M.B., Iglesias-Vilas, G., Liz-Marzan, L.M., Blanco-Mendez, J., Lopez Quintela, M.A., Marty, J.P., Guy, R.H., 1997. Delivery of a hydrophilic solute through the skin from novel microemulsion systems. Eur. J. Pharm. Biopharm. 43, 37–42.

Djordjevic, L., Primorac, M., Stupar, M., Krajisnik, D., 2004. Characterization of caprylocaproyl macrogolglycerides based microemulsion drug delivery vehicles for an amphiphilic drug. Int. J. Pharm. 271, 11–19.

Engehausen, K., Müeller-Goymann, C.C., 1992. Diclofenac diethylamine permeation from microemulsions and liposomes through human stratum corneum. In: Proceedings of the Second Lip. Res. Days, Leiden.

Gašperlin, M., Špiclin, P., 2001. Caprylocaproyl macrogolglycerides based microemulsions: physicochemical and phase behaviour properties. Sci. Pharm. 69, 157–158.

Gattefossé, S.A., 1994. Microemulsions: Formulation Guide, publication No. PF9225 A, Saint-Priest Cedex, France.

Grassi, M., Coceani, N., Magarotto, L., 2000. Mathematical modeling of drug release from microemulsions: theory in comparison with experiments. J. Colloid Interface Sci. 228, 141–150.

Kahlweit, M., Strey, R., Haase, D., Kunieda, H., Schmeling, T., Faulhaber, B., Borkovec, M., Eicke, H.-F., Busse, G., Eggers, F., Funck, Th., Richmann, H., Magid, L., Söderman, O., Stilbs, P., Winkler, J., Dittrich, A., Jahn, W., 1987. How to study microemulsions. J. Colloid Interface Sci. 118, 436–453.

Kibbe, A.H., 2000. Handbook of Pharmaceutical Excipients, 3rd ed. Pharmaceutical Press, London.

Kreilgaard, M., Kemme, M.J., Burggraaf, J., Schoemaker, R.C., Cohen, A.F., 2001. Influence of a microemulsion vehicle on a cutaneous biequivalence of a lipophilic model drug assesed by microdialysis and pharmacodinamics. Pharm. Res. 18, 593–599.

Kreilgaard, M., Pedersen, E.J., Jaroszewski, J.W., 2000. NMR characterization and transdermal drug delivery potential of microemulsion systems. J. Control. Release 69, 421–433.

Kriwet, K., Müeller-Goymann, C.C., 1993. Binary diclofenac diethylamine–water systems: micelles, vesicles and lyotropic liquid crystals. Eur. J. Pharm. Biopharm. 39, 234–238.

Kriwet, K., Müeller-Goymann, C.C., 1995. Diclofenac release from phospholipid drug systems and permeation through excised human stratum corneum. Int. J. Pharm. 125, 231–242.

Kumar, P., Mital, K.L., 1999. Handbook of Microemulsion: Science and Technology. Marcel Dekker, New York, Basel.

Lawrence, M.J., Rees, G.D., 2000. Microemulsion-based media as novel drug delivery systems. Adv. Drug Deliv. Rev. 45, 89–121.

Ledvige, M.T., Corrigan, O.I., 1998. Effects of surface active characteristics and solid state forms on the pH solubility profiles of drug–salt systems. Int. J. Pharm. 17, 187–200.

Lehmann, L., Keipert, S., Gloor, M., 2001. Effects of microemulsions on the stratum corneum and hydrocortisone penetration. Eur. J. Pharm. Biopharm. 52, 129–136.

Müeller-Goymann, C.C., Kriwet, K., Eder, I., Papantoniou, I., 1995. Microemulsions and related systems for the dermal application of drugs. B.T. Gattefosse 88, 43–54.

Parsaee, S., Sarbolouki, M.N., Parnianpour, M., 2002. In-vitro release of diclofenac diethylammonium from lipid-based formulations. Int. J. Pharm. 241, 185–190.

Schmalfuß, U., Neubert, R., Wohlrab, W., 1997. Modification of drug penetration into human skin using microemulsions. J. Control. Release 46, 279–285.

Sirotti, C., Coceani, N., Colombo, I., Lapasin, R., Grassi, M., 2002. Modeling of drug release from microemulsions: a peculiar case. J. Membr. Sci. 204, 401–412.

Spiclin, P., Homar, M., Zupancic-Valant, A., Gasperlin, M., 2003. Sodium ascorbyl phosphate in topical microemulsions. Int. J. Pharm. 256, 65–73.

Strey, R., 1996. Microemulsion microstructure. Euro Cosmet. 10, 39–46.

Trotta, M., Morel, S., Gasco, M.R., 1997. Effect of oil phase composition on the skin permeation of felodipine from O/W microemulsions. Pharmazie 52, 50–53.