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Effect of Oil Phase Lipophilicity on In Vitro Drug Release from O/W Microemulsions with Low Surfactant Content

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ABSTRACT In this work we investigated the effects of oil phase lipophilicity on in vitro drug release from topical o/w microemulsions (MEs) containing low percentages of emulsifiers. Three different lipids, isopropyl myristate (IPM), isopropyl palmitate (IPP), and isopropyl stearate (IPS), whose lipophilicity increased in the order IPM < IPP <IPS, were used as oil phase to prepare o/w MEs containing low amounts (7.7% w/w) of two surfactant/cosurfactant mixtures, isoceteth-20/glyceryl oleate (5:2) (MEs 1–3) and oleth-20/glyceryl oleate (5:2) (MEs 4–6). All the MEs were prepared using the phase inversion temperature (PIT) method.

Three active compounds (0.5% w/w), Naproxen (NAP), Idebenone (IDE), and Butylmethoxydibenzoylmethane (BMBM), were selected as model drugs and their release rates from PIT MEs were evaluated using Franz-type diffusion cells. All the MEs gave a mean droplet diameter ranging from 28 to 44 nm and showed a single peak in size distribution. The addition of IDE to MEs 1–6 did not significantly change ME droplet size. On the contrary, an increase of the droplet size beyond the ME limit (150 nm) was observed when isoceteth-20 was used as surfactant to prepare MEs containing NAP or MEs containing BMBM and IPS as oil phase. Pseudo-first order release rates were observed only for NAP from MEs 1–3, while MEs containing IDE showed an initial slow release followed by an increased release of the test compound. The release rate constants were found to be dependent on the ME composition and on the active compound incorporated. The highest release rate was observed from ME 1 containing IPM as oil phase and NAP as drug. As regards BMBM, its release rate was not calculated since no release was observed until 6 h from the beginning of the experiment. The cumulative amount of active compound released after 22 h was inversely related to drug lipophilicity (NAP Log P = 2,9; IDE Log P 3,5; BMBM Log P 4,8). These findings could be attributable to a reduced thermodynamic activity of the drugs in the vehicles containing the most lipophilic oil phase due to an increase of drug solubility which could lead to an unfavorable drug partition from the oil phase. The results of this study suggest that the choice of proper combinations of oil

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phase lipids and emulsifiers may allow achieving drug controlled delivery from topical o/w MEs with low emulsifier content.

KEYWORDS PIT microemulsions, Topical drug delivery, in vitro release, Surfactants, Oil phase lipophilicity

INTRODUCTION

Recently, microemulsions (MEs) have received great attention as topical drug delivery systems. Microemulsions (MEs) are transparent, thermodynamically stable, low viscosity, and isotropic dispersions with droplet size in the submicron range. They typically consist of an aqueous phase, an oil phase, and an emulsifier system which ensures the formulation stability due to its ability to lower interfacial tension (Philip et al., 2003; Schmalfub et al., 1997; Trotta et al., 2003).

Because of their ease of manufacturing, their ability to incorporate a wide range of compounds of different lipophilicity and to enhance drug skin penetration (Kreilgaard, 2002; Gasco, 1997), MEs represent an interesting vehicle for topical application in order to improve drug topical efficacy while reducing systemic absorption and unwanted side effects.

Many studies have pointed out the influence of the oil phase composition and of the type of emulsifiers used on the properties of topical MEs (Trotta et al., 1997; Aboofazeli et al., 1994). Therefore, a great variety of lipids and surfactants, in different concentrations, have been tested to establish their influence on droplet size, drug loading, system stability, and drug delivery. Microemulsions (MEs) containing different lipids and concentrations ranging from 25% to 47% of different emulsifiers were proposed as vehicles to improve estradiol delivery after topical administration (Peltola et al., 2003). A microemulsion (ME) constituted of isopropyl myristate (IPM) as lipid, Tween80 (30.8%) as surfactant, and benzyl alcohol (11.75%) as cosurfactant was developed to increase topical release of Nimesulide (Sirotti et al., 2002). Different MEs were prepared using high percentages (30%, 55% or 80%) of Labrasol/Cremophor RH 40 (1:1) as emulsifier system in order to achieve maximum skin permeation rates of Ketoprofen (Rhee et al., 2001).

However, the requirement of high concentrations of surfactants (from 25% up to 80%) and the use of substances like benzyl alcohol, widely recognized to be an irritant for the skin, have limited the pharmaceutical applications of MEs.

Recent studies have shown the feasibility of using the phase inversion temperature (PIT) as a method to prepare oil-in-water microemulsions containing low percentages of surfactant (Diec et al., 2001). The phase inversion temperature (PIT) value depends on the characteristics of the oils and the surfactants used, in addition to the presence of lipophilic drugs which can decrease the PIT value (Izquierdo et al., 2005). Phase inversion temperature (PIT) MEs could be prepared using amounts of surfactants as low as those employed to prepare conventional emulsions, thus allowing to overcome the problems connected with the irritating effect of high quantity of surfactants.

An essential requisite for a topical formulation to be successful is a suitable drug delivery so as to achieve effective drug percutaneous absorption. However, to date, little work has been done to assess drug release and skin permeation from PIT MEs.

The aim of this study was to investigate the effects of oil phase lipophilicity on drug release from topical MEs with low content of emulsifiers. Three different lipids, isopropyl myristate (IPM), isopropyl palmitate (IPP), and isopropyl stearate (IPS), whose lipophilicity increased in the order IPM < IPP < IPS, were used as oil phase to prepare o/w MEs containing low amounts (7.7% w/w) of two surfactant/cosurfactant mixtures, isoceteth-20/glyceryl oleate (5:2) and oleth-20/glyceryl oleate (5:2). Nonionic surfactants were used since they are regarded as less toxic than ionic ones. In order to study the effects of different MEs compositions on in vitro drug release, three active compounds with different partition coefficient were selected: Naproxen (NAP), one of the most commonly used non-steroidal anti-inflammatory drugs; Idebenone (IDE), an antioxidant agent under investigation for topical use; and Butylmethoxydibenzoylmethane (BMBM), a lipophilic UVA filter widely used in sunscreen preparations.

MATERIALS AND METHODS

Naproxen (NAP), polyoxyethylene-20-oleyl ether (oleth-20, Brij 98), and polyoxyethylene-20- isohexadecyl ether (isoceteth-20, Arlasolve 200) were purchased from Sigma (Milan, Italy). Glyceryl oleate (Tegin O) was obtained from Th. Goldschmidt Ag (Milan, Italy). Isopropyl myristate (IPM), isopropyl palmitate (IPP), and isopropyl stearate (IPS) were bought from ACEF (Milan, Italy). Idebenone (IDE) was a kind gift of Wyeth Lederle

(Catania, Italy). Butylmethoxydibenzoylmethane (BMBM) was kindly supplied by Basf (Ludwigshafen, Germany).

Regenerated cellulose membranes (Spectra/Por CE; Mol. Wet. Cut off 3,000) were supplied by Spectrum (Los Angeles, CA).

Acetonitrile, methanol, and water used in the HPLC procedures were of LC grade and were bought from Merck (Milan, Italy). All other reagents were of analytical grade.

Preparation of O/W Microemulsions

Microemulsions (MEs) were prepared using the PIT method (Diec et al., 2001). The composition of formulations 1–6 is shown in Table 1. The aqueous phase and the oil phase were separately heated at 80–90°C; then the aqueous phase was added drop by drop, at constant temperature and under agitation, to the oil phase. The formulation was then cooled to room temperature under slow and continuous stirring.

At the PIT, the turbid mixture turned into a clear "bluish-white" o/w ME. The phase inversion temperature (PIT) was determined using a Crison 525 conductivity meter which measured an electric conductivity change when the inversion from w/o to o/w ME occurred. To prepare the MEs containing active ingredients, one of the selected drugs (0.5% w/w), NAP, IDE, or BMBM, was added.

Physico-chemical parameters (molecular weight and logP) of drugs and lipids used to obtain MEs 1–6 are reported in Table 2.

Photon Correlation Spectroscopy (PCS)

The droplet sizes of the MEs tested were determined using a ZETAMASTER S (Malvern Instruments, Malvern, UK), at 20°C, by scattering light at 90°. The instrument performed particle sizing by means of a 4 mW laser diode operating at 670 nm. The values of the mean diameter and polydispersity index were the averages of results obtained for two separate preparations.

Stability Tests

Samples of MEs 1–6 were stored in airtight jars, and then kept in the dark at room temperature for two months.

The droplet size and the polydispersity index of the samples were measured at fixed time intervals (one week, two weeks, one month, and two months) after their preparation.

In vitro Release Experiments

Active compound release rates from the MEs being tested were measured through cellulose membranes by means of Franz-type diffusion cells (LGA, Berkeley, CA). This technique has been previously reported in the literature as a suitable method for evaluating drug release from topical formulations (Shah et al., 1989).

The cellulose membranes were moistened by immersion in water for 1 h at room temperature before being mounted in Franz-type diffusion cells. The cells had a diffusion surface area of 0.75 cm^2 and a 4.5 mL receiving chamber which was filled with water/ethanol (50/50 v/v) for ensuring pseudo-sink conditions by increasing active compound solubility in the receiving phase (Touitou & Fabin, 1988). The receiving solution fluid was constantly stirred (700 rpm) and thermostated at 35°C so as to maintain the membrane surface at 32°C. Each formulation (500 μL) was applied on the membrane surface and the experiments were run for 22 h. Due to IDE and BMBM

TABLE 1 Composition (% w/w) of MEs 1–6

ME	Oleth-20	Isoceteth-20	Glyceryl oleate	IPM	IPP	IPS	Water[1]
1	5.5	/	2.2	5	/	/	87.3
2	5.5	/	2.2	/	5	/	87.3
3	5.5	/	2.2	/	/	5	87.3
4	/	5.5	2.2	5	/	/	87.3
5	/	5.5	2.2	/	5	/	87.3
6	/	5.5	2.2	/	/	5	87.3

[1]Water containing 0.35% w/w imidazolidinyl urea and 0.05% w/w Kathon CG was used.

TABLE 2 **Physico-chemical Parameters (Molecular Weight and Log P) of Active Compounds and Lipids Used to Prepare MEs 1–6**

Compound	Molecular weight	Log P[1]
NAP	230,26	2,998 ± 0,239
IDE	338,44	3,491 ± 1,000
BMBM	310,39	4,806 ± 0,345
IPM	270,45	7,432 ± 0,212
IPP	298,50	8,495 ± 0,213
IPS	326,56	9,557 ± 0,213

[1]Log P was obtained from Advanced Chemistry Development (ACD) Software Solaris V 4.67.

photoinstability, all the release experiments were carried out avoiding light exposure. At intervals, samples of the receptor phase (200 μL) were withdrawn and replaced with an equal volume of receiving solution equilibrated to the experimental temperature (35°C). The samples of the receptor phase were analyzed by the HPLC method described below to determine their active compound content. At the end of the experiments, samples of the ME applied on the membrane surface were withdrawn and analyzed to determine ME droplet sizes and polydispersity indexes. Each experiment was performed in triplicate.

High Performance Liquid Chromatography (HPLC) Analyses

A Varian model 9010 liquid chromatographic system (Varian, Milan, Italy) equipped with a model 9020 UV-Vis detector, a 20 μL Rheodyne model 7125 injection valve, and a recorder Varian 4010 was used. The chromatographic analyses were performed using a Waters Simmetry, 4.6 × 15 cm reverse phase column (C_{18}) at room temperature. The mobile phase consisted of an acetonitrile/water mixture (80:20 v/v) for BMBM analysis, an acetonitrile/water mixture (70:30 v/v) for IDE analysis, and a methanol/phosphate buffer pH 2.5 (65:35 v/v) for NAP analysis. The column effluent (flow rate 1 mL/min) was monitored continuously at 274 nm to detect NAP, at 284 nm to detect IDE, and at 360 nm to detect BMBM. The amounts of each compound were calculated by reporting the peak area of a sample on a standard calibration curve that was built up by relating known concentrations of NAP, IDE, and BMBM with the respective peak areas. No interference of the other formulation components was observed. The sensitivity of the HPLC method was 0.1 μg/mL for all the compounds tested.

Data analysis

The transfer rate constants (k) of the active compound between the oil droplet and the aqueous phase were calculated according to a model which considers the rate of release to be limited by an interfacial barrier (Guy et al., 1982) using the following equation:

$$\ln (1 - M_t/M_o) = -\frac{-3kt}{r^2}$$

where M_t/M_o is the fraction of released drug at time t and r is the droplet radius. Plotting the natural logarithm of the fraction of released drug against time, release curves whose slope was $-3k/r^2$ were obtained.

Active compound apparent diffusion coefficients (D_{app}) through cellulose membranes were calculated according to the relation:

$$D_{app} = \frac{h^2}{6t_L}$$

where h is the thickness of the membrane (25 nm) and t_L is the lag time. The lag time was calculated by plotting the cumulative amount of compound released against time and dividing the slope of the steady-state portion of the graphs by the area through which diffusion took place. The lag time was determined from the x-intercept values of the regression lines.

Results are expressed as mean values ± standard deviation (SD). Statistical data analysis was performed using a one-way ANOVA with a posteriori Bonferroni's t-test.

RESULTS AND DISCUSSION

Microemulsion Formulations

The percentages of surfactant and cosurfactant required to obtain a ME containing 5% of oil phase were determined from preliminary experiments showing that 5.5% of surfactant and 2.2% of cosurfactant were the lowest amounts required.

As reported in Table 3, all the MEs without active compound gave a mean droplet size between 28 nm

TABLE 3 Droplet Size (Size ± S.D.), Polydispersity Index (Poly ± S.D.), and PIT of MEs 1–6 Without Active Compound

ME	PIT (°C)	Size ± S.D. (nm)	Poly ± S.D.
1	75	28,6 ± 0,3	0,275 ± 0,005
2	75	28,3 ± 0,5	0,231 ± 0,016
3	75	30,1 ± 0,6	0,447 ± 0,022
4	60	36,3 ± 0,5	0,234 ± 0,005
5	60	44,5 ± 0,7	0,467 ± 0,009
6	60	32,2 ± 0,8	0,209 ± 0,012

and 44 nm and showed a single peak in size distribution. No relationship was observed between droplet size and oil phase lipophilicity. Other authors (Moulik et al., 1998) found that ME droplet size changed depending on the partition coefficient of the oil phase. The results obtained for MEs 1–6 suggest that only a weak interaction between the oil component and the structure of the interfacial layer of surfactants may occur. On the contrary, the use of different surfactants affected ME droplet size since MEs prepared using oleth-20 had droplets smaller than the corresponding MEs obtained using isoceteth-20. The different structure of the acyl chain of these surfactants could determine different packing of the surfactant and cosurfactant molecules at the interface, leading to droplets with a different curvature radius.

The phase inversion temperatures (PIT), or HLB temperature, of MEs obtained using oleth-20 as surfactant (MEs 1–3) were higher than those observed for MEs 4–6 containing isoceteth-20 (see Table 3). These results could be due to the different HLB values of oleth-20 (HLB = 15,3) and isoceteth-20 (HLB = 15,7). Similar findings have been reported by Izquierdo et al. (2005) studying the influence of nonionic ethoxylated surfactants on nano-emulsion formation by the PIT emulsification method. These authors reported a linear variation of PIT values with surfactant HLB number. As shown in Table 3, PIT values were not affected by the lipophilicity of the oil phase, thus suggesting weak interactions between the oil phase component and the surfactant interfacial layer.

From the data reported in Table 3, a greater stability of MEs 1–3 would be expected since their PIT values were higher than those observed preparing MEs 4–6. As reported in literature (Foster et al., 1990), at PIT the emulsification process is favored due to the low values of interfacial tension but the emulsion stability is low since fast coalescence of the droplets occurs. Therefore, the higher the difference between PIT and the storage temperature, the higher the emulsion stability (Izquierdo et al., 2005). However, stability tests performed at room temperature did not show any significant change of droplet size and polydispersity index for all the MEs under investigation (Fig. 1). Stability tests performed on MEs loaded with active compounds provided results similar to those observed for unloaded MEs (data not shown).

The addition of NAP to MEs 1–3 did not affect PIT values and mean droplet size (see Table 4). When isoceteth-20 was used as surfactant (MEs 4–6) the addition of NAP leads to an emulsion rather than an ME (data not shown). Microemulsions (MEs) prepared using IDE as active compound showed an increase of PIT values without any significant change of droplet size compared to the corresponding control (ME without active compound). As regards BMBM, its addition to MEs 1–3 increased their PIT values without affecting ME droplet sizes. The incorporation of BMBM into MEs containing isoceteth-20 as surfactant lead to higher PIT values and to an increase of droplet sizes that was dependent on the oil phase lipophilicity. A microemulsion (ME) could not be obtained using isoceteth-20 and IPS as oil phase when 0.5% w/w of BMBM was incorporated into the formulation. As reported in the literature (Izquierdo et al., 2005), an increase of surface or interfacial activity provides emulsions or ME with reduced droplet sizes. All the model drugs under investigation did not seem to affect surface or interfacial activity when oleth-20 was used as surfactant since no change of droplet radii was observed by adding NAP, IDE, or BMBM to MEs 1–3. However, while the addition of NAP to MEs 1–3 did

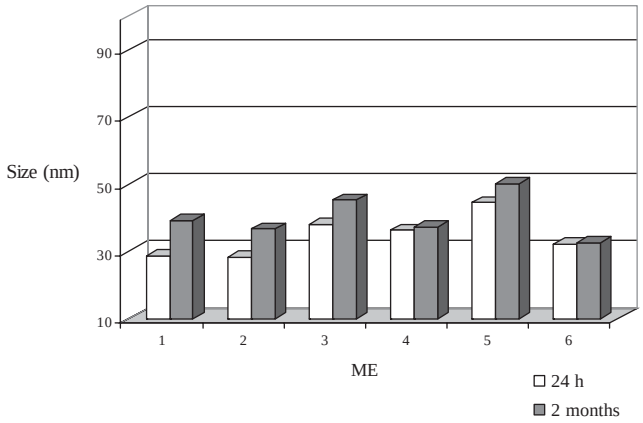

FIGURE 1 Droplet Size of MEs 1–6 24 h After Their Preparation and After 2 Months of Storage at Room Temperature.

TABLE 4 Droplet Size (Size ± S.D.), Polydispersity Index (Poly ± S.D.), and PIT of MEs 1–6 containing NAP, IDE, and BMBM

Compound	ME	PIT (°C)	Size ± SD (nm)	Poly ± SD
NAP	1	75	24,5 ± 0,2	0,280 ± 0,010
	2	75	23,0 ± 0,1	0,258 ± 0,019
	3	75	23,9 ± 0,5	0,279 ± 0,056
IDE	1	78	26,4 ± 0.8	0,204 ± 0.007
	2	78	28,1 ± 0.6	0,271 ± 0.013
	3	78	27,2 ± 0,2	0,288 ± 0,020
	4	65	40,8 ± 1,0	0,290 ± 0,019
	5	65	41,2 ± 0,3	0,366 ± 0,018
	6	65	38,4 ± 0,4	0,284 ± 0,011
BMBM	1	80	29,7 ± 0,5	0,286 ± 0,014
	2	80	31,7 ± 0,1	0,465 ± 0,015
	3	80	28,7 ± 0,3	0,241 ± 0,019
	4	70	46,9 ± 0,9	0,263 ± 0,012
	5	70	64,6 ± 1,9	0,329 ± 0,019

not affect PIT values, the incorporation of IDE or BMBM caused an increase of PIT values. These findings could be explained by a partial self-aggregation of the most lipophilic IDE or BMBM molecules leading to formation of micelles surrounded by a layer consisting mostly of the less hydrophilic surfactant. In this way, an increase of the most hydrophilic surfactant in the aqueous phase could be produced causing an increase of PIT values (Izquierdo et al., 2005). As regards MEs 4–6, the addition of NAP, IDE, or BMBM caused an increase of both droplet sizes and PIT values. These results suggest that these drugs decreased surface or interfacial activity likely causing, at the same time, an increase of the most hydrophilic surfactant content in the aqueous phase. Since MEs loaded with IDE or BMBM showed higher PIT values than the corresponding MEs without active compound, a great stability of loaded MEs would be expected. However, no significant effect of drug addition on MEs stability was observed likely due to the short period of storage.

These results suggest different interactions of the active compounds being tested with the surfactant/cosurfactant layer at the droplet interface leading to change of fluidity of the interfacial surfactant film and of the field of existence of the ME.

In vitro Release Experiments

One of the most important features of a pharmaceutical colloidal system is its drug delivery profile which describes the process of drug diffusion out of the vehicle after administration.

In this work we assessed in vitro drug release from topical o/w MEs using the infinite dose technique, i.e., applying a large amount of formulation (500 μL) on the membrane surface. The use of an infinite dosing in in vitro release studies avoids compound depletion from the donor compartment during the experiment thus ensuring a constant driving force for the release process and allowing the achievement of steady-state conditions. Previous studies (Walters et al., 1997) on in vitro percutaneous penetration of octyl salycilate from sunscreen formulations did not show any significant difference of the percentage of the applied dose of UV-filter permeated from the same formulations using a finite or an infinite dose technique.

In vitro release profiles of NAP, IDE, and BMBM from MEs with low surfactant content are depicted in Figs. 2–4. Plotting the cumulative amount of NAP

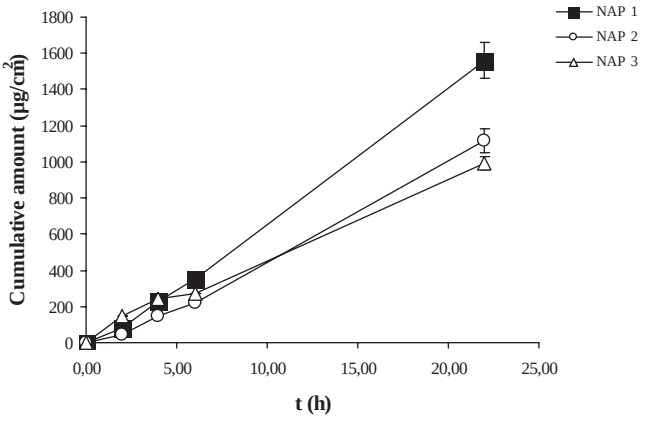

FIGURE 2 Release Profiles of NAP Through Cellulose Membranes from MEs 1–3. For Clarity, Error Bars Are Reported Only for Data at 22 h.

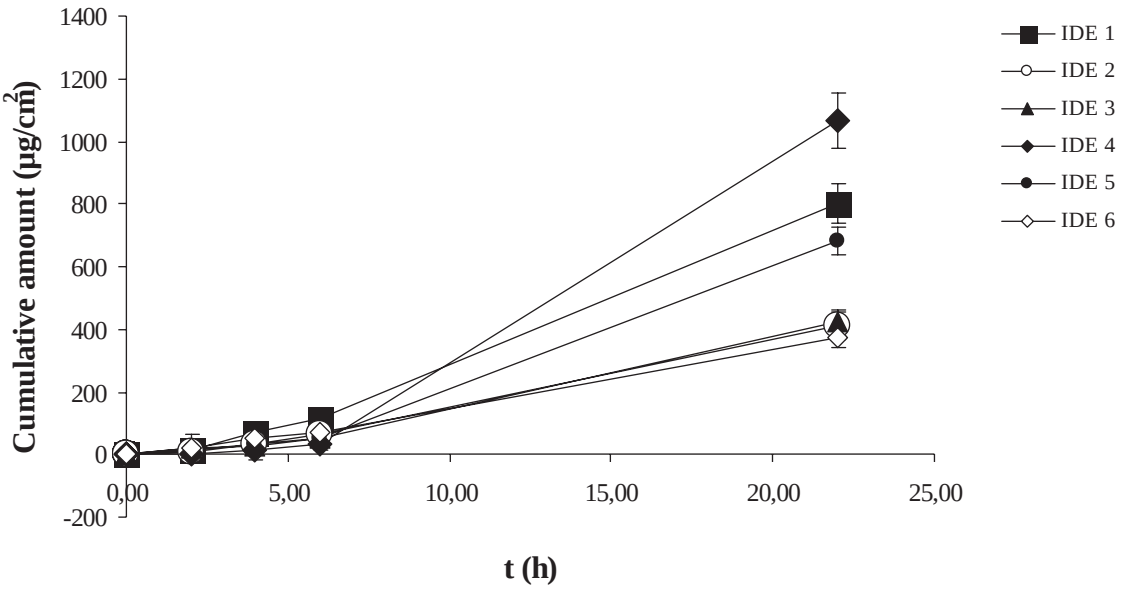

FIGURE 3 **Release Profiles of IDE Through Cellulose Membranes from MEs 1–6. For Clarity, Error Bars Are Reported Only for Data at 22 h.**

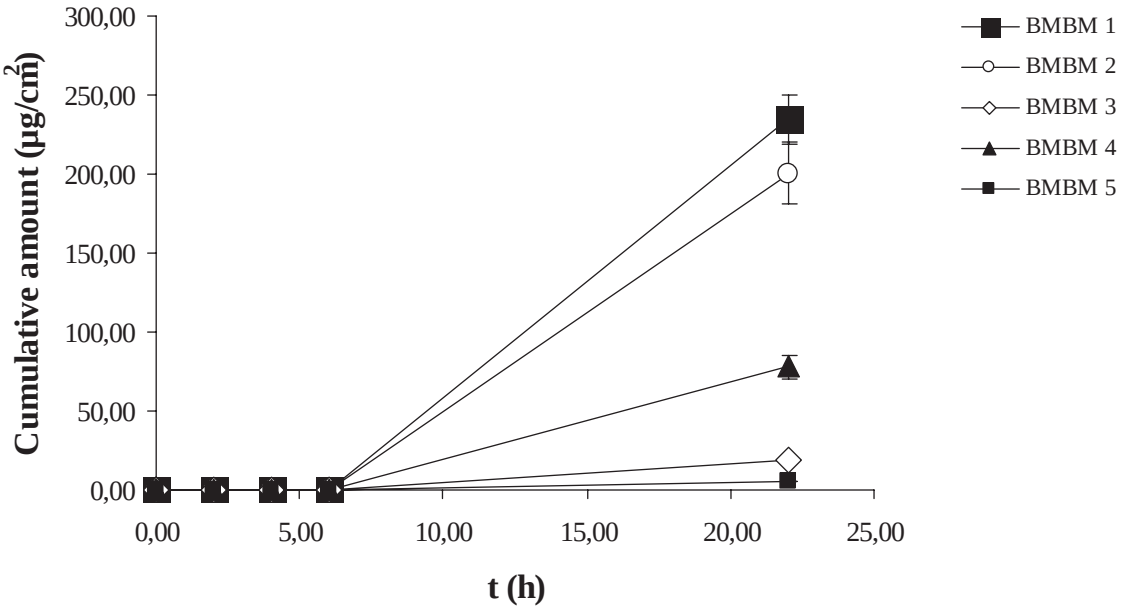

FIGURE 4 **Release Profiles of BMBM Through Cellulose Membranes from MEs 1–5. For Clarity, Error Bars Are Reported Only for Data at 22 h.**

released after 22 h from MEs 1–3 as a function of time, a linear relationship ($r > 0.99$) was obtained (Fig. 2). Naproxen (NAP) release from MEs 4–6 was not determined since these formulations could not be regarded as MEs due to their large droplet sizes (>150 nm). Microemulsions (MEs) containing IDE showed different release profile depending on ME composition (Fig. 3). An initial slow release followed by an increase of IDE release was observed from ME 1 and 4 both containing IPM as oil phase. Therefore, steady-state conditions from ME 1 and 4 were achieved later compared to MEs 2, 3, 5, and 6 when IDE was incorporated in the formulation. However, also for MEs containing IDE, linear relationships ($r > 0.98$) were obtained by plotting the amount of drug released against time. As regards to BMBM, no release was observed until 6 h from the beginning of the experiment, but after 22 h different amounts of BMBM were found in the receiving phase depending on the vehicle composition.

TABLE 5 Release Rate Constants (K), Apparent Diffusion Coefficients (D_{app}), and Cumulative Amount Released After 22 h ($Q_{22} \pm SD$) of NAP, IDE, and BMBM

Compound	ME	$Q_{22} \pm$ S.D. (μg)	$K \times 10^{-3}$ ($nm^2\ sec^{-1}$)	$D_{app} \times 10^3$ ($nm^2\ sec^{-1}$)
NAP	1	1560,00 ± 98,23	0,68	42,55
	2	1116,94 ± 67,55	0,35	26,31
	3	991,76 ± 34,15	0,28	38,58
IDE	1	801,06 ± 62,66	0,29	18,31
	2	413,39 ± 43,62	0,13	17,97
	3	420,64 ± 38,57	0,11	18,43
	4	1065,40 ± 90,44	0,99	11,48
	5	682,42 ± 43,15	0,49	13,91
	6	372,13 ± 30,55	0,28	34,86
BMBM	1	234,49 ± 16,04	N.D.[a]	N.D.[a]
	2	200,58 ± 19,35	N.D.[a]	N.D.[a]
	3	19,30 ± 0,83	N.D.[a]	N.D.[a]
	4	78,07 ± 7,25	N.D.[a]	N.D.[a]
	5	5,37 ± 0,36	N.D.[a]	N.D.[a]

[a]Not determined since no release was observed until 6 h from the beginning of the experiment.

In order to explain the observed profiles of release of NAP and IDE, we calculated the transfer rate constants (K) from oil phase droplets and the apparent diffusion coefficients (D_{app}) through cellulose membranes (Table 5).

These parameters could not be calculated for BMBM since no release was detected up to 6 h and therefore no release curve could be drawn. As shown in Table 5, NAP and IDE D_{app} values were in the same order of magnitude for all the tested MEs and were notably higher (six orders of magnitude) than the corresponding transfer rate constants. These results show that the rate-limiting step for in vitro drug release from the MEs under investigation was drug diffusion out of the oil phase droplets rather than drug diffusion through the cellulose acetate membrane. The observed transfer rate constants were consistent with an interfacial barrier being the rate-limiting step for drug release. The existence of an interfacial barrier to drug release from ME oil phase droplets has already been reported for ME containing indomethacin as active compound (Trotta, 1999). Transfer rate constants were dependent on the oil phase Log P although no linear relationship was observed. As shown in Figs. 5 and 6, the release profile of NAP and IDE out of the oil phase droplets was similar although different interactions between drug and vehicle components may occur since the addition of NAP to MEs 4–6 lead to an emulsion rather than to an ME, and NAP K values were higher than those obtained for IDE from the corresponding MEs. The same concentration of IDE and NAP was added to MEs 1–6, therefore, their molar ratios were different due to their different molecular weight (see Table 1). The higher molar ratio and the lower Log P of NAP could lead to changes of the packing of the surfactant molecules at the interface due to a different localization of the drug within the surfactant layer. As reported by Carlotti et al. (1995), the structure of the interface in the MEs may play an important role in determining the barrier properties to drug diffusion out of the oil droplets.

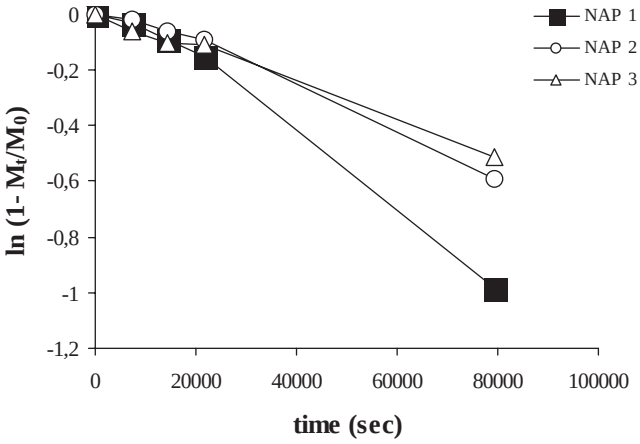

FIGURE 5 Natural Logarithm of the Amount of NAP Remaining in the Oil Droplet Against Time from MEs 1–3.

In our study, both the nature of the surfactant and lipophilicity of the oil phase had a doubtful influence on active compound release. As shown in Table 5, the cumulative amount of active compound

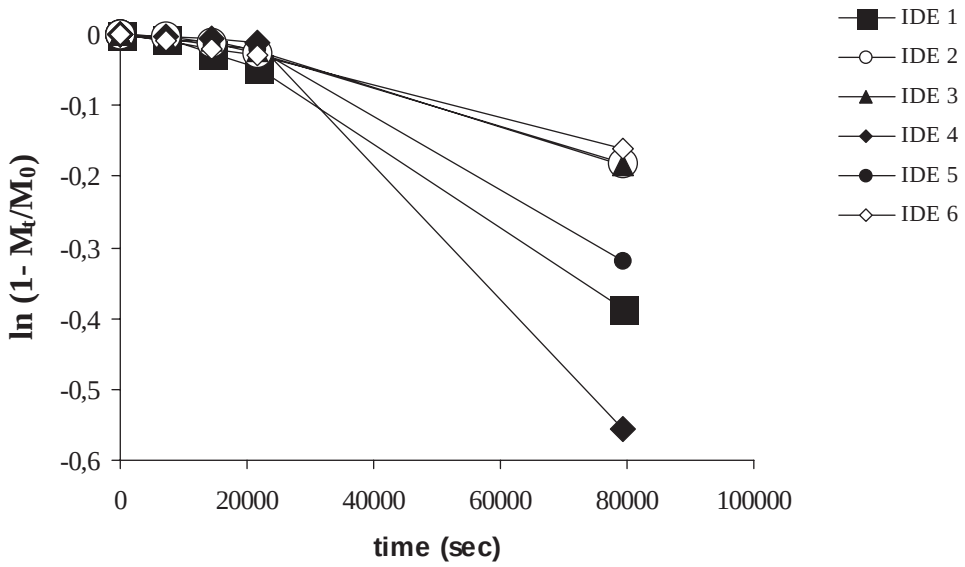

FIGURE 6 **Natural Logarithm of the Amount of IDE Remaining in the Oil Droplet Against Time from MEs 1–6.**

released after 22 h was inversely related to the drug lipophilicity since the higher the drug partition coefficient, the lower the amount of drug released at the end of the experiment. These findings could be due to a reduced thermodynamic activity of the drugs in the vehicles containing the most lipophilic oil phase due to an increase of drug solubility, which could lead to an unfavorable partition from the oil phase. Similar findings have been reported by Dreher et al. (1997) comparing lecithin-based ME gel to IPP as a vehicle for transdermal delivery of two anti-inflammatory drugs. These authors attributed the lower skin permeability coefficients obtained from ME formulations to an unfavorable drug partition coefficient from this vehicle due to a lower drug thermodynamic activity.

The different release profile obtained from MEs with low emulsifier content could be exploited for pharmaceutical and cosmetic applications. In fact, for a successful therapy with an antioxidant or an anti-inflammatory drug, their delivery from the formulation should be controlled so as to provide the skin with therapeutically effective amounts of the drug. On the other hand, as far as sunscreen agents are concerned, the vehicle should keep the UV-filter on the skin surface, where it has to carry out its activity, thus reducing the risks of side effects due to its systemic absorption. The results of our study show that BMBM release from MEs containing low amounts of surfactants was negligible up to 6 h after application of the vehicle on the membrane surface. A similar profile of release could be useful to improve the efficacy and the safety of sunscreen products. On the other hand, drugs such IDE and NAP could benefit from the use of MEs with low surfactant content since drug release may be modulated by the use of different oil and surfactant combinations.

Recently, nonionic surfactants have been reported to modify the skin barrier function (Lopez et al., 2000; Fang et al., 2001), therefore, drug skin permeation after topical administration of ME may depend on surfactant enhancement effects, in addition to drug release profile from the vehicle. Further studies are ongoing in order to investigate the mechanisms of drug delivery into the skin from MEs with low surfactant content.

CONCLUSIONS

This study investigated the effects of oil phase lipophilicity on in vitro drug release from MEs prepared using low amounts of emulsifier systems. Different release profiles were obtained depending on oil phase lipophilicity, drug partition coefficients, and type of surfactant used. Therefore, MEs containing low amounts of surfactants could be proposed as vehicles in order to achieve drug controlled delivery by choosing proper combinations of oil phase lipids and emulsifier systems.

REFERENCES

Aboofazeli, R., Lawrence, C. B., Wicks, M. J., & Lawrence, M. J. (1994). Investigations into the formation and characterization of phospholipid microemulsions III. Pseudo-ternary phase diagrams of systems containing water-lecithin-isopropyl myristate and either an alkanoic acid, amine, alkanediol, polyethylene glycol alkyl ether or alcohol as co-surfactant. *Int. J. Pharm*., *111*, 63–72.

Carlotti, M. E., Trotta, M., & Gasco, M. R. (1995). Influence of some components of emulsions and microemulsions on the oxidation of linoleic acid and ethyl linoleate. *STP Pharma Sci*., *5*, 379–383.

Diec, K. H., Eitrich, A., Schmidt, T., Sokolowski, T., & Screeber, J. (2001). PIT Microemulsions with low surfactant content. *Cosmetic & Toiletries*, *116*, 61–66.

Dreher, F., Walde, P., Walther, P., & Wehrli, E. (1997). Interaction of a lecithin microemulsion gel with human stratum corneum and its effect on transdermal transport. *J. Controlled Rel*., *45*, 131–140.

Fang, J. Y., Yu, S. Y., Wu, P. C., Huang, Y. B., & Tsai, Y. H. (2001). In vitro skin permeation of estradiol from various proniosome formulations. *Int. J. Pharm*., *215*, 91–99.

Foster, J., Schambil, L., & Tessman, P., (1990). Emulsification by the phase inversion temperature method: the role of self-bodying agents and influence of oil polarity. *Int. J. Cosm. Sci*., *12*, 217–227.

Gasco, M. R. (1997). Microemulsions in the pharmaceutical field: perspective and application. In *Industrial Applications of Microemulsions*; Solans, C., Kunieda, H. Eds; Marcel Dekker, Inc.: New York; 97–122.

Guy, R. H., Hadgraft, J., Kellaway, I. W., & Taylor, M. J. (1982). Calculations of drug release rates from spherical particles. *Int. J. Pharm*., *11*, 199–207.

Izquierdo, P., Feng, J., Esquena, J., Tadros, T. F., Dederen, J. C., Garcia, M. J., Azemar, N., & Solans, C. (2005). The inflence of surfactant mixing ratio on nano-emulsion formation by the PIT method. *J. Colloid Interface Sci*., *285*, 388–394.

Kreilgaard, M. (2002). Influence of microemulsions on cutaneous drug delivery. *Adv. Drug Del. Rev*., *54*, S77–S98.

Lopez, A., Linares, F., Cortell, C., & Herràez, M. (2000). Comparative enhancer effects of Span 20 with Tween 20 and Azone on the in vitro percutaneous penetration of compounds with different lipophilicities. *Int. J. Pharm*., *202*, 133–140.

Moulik, S. P., & Paul, B. K. (1998). Structure, dynamics and transport properties of microemulsions. *Adv. Colloid Interface Sci*., *78*, 99–195.

Peltola, S., Saarinen-Savolainen, P., Kiesvaara, J., Suhonen, T. M., & Urtti, A. (2003). Microemulsions for topical delivery of estradiol. *Int. J. Pharm*., *254*, 99–107.

Philip, J. L., Langer, R., & Prasad Shastri V. (2003). Novel microemulsion enhancer formulation for simultaneous transdermal delivery of hydrophilic and hydrophobic drugs. *Pharm. Res*., *20*, 264–269.

Rhee, Y. S., Choi, J. G., Park, E. S., & Chi, S. C. (2001). Transdermal delivery of ketoprofen using microemulsions. *Int. J. Pharm*., *228*, 161–170.

Schmalfub, U., Neubert, R., & Wohlrab, W. (1997). Modification of drug penetration into human skin using microemulsions. *J. Control. Rel*., *46*, 279–285.

Shah, V. P., Elkins, J., Lam, S. Y., & Skelly, J. P. (1989). Determination of in vitro drug release from hydrocortisone creams. *Int. J. Pharm*., *53*, 53–59.

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.

Touitou, E., & Fabin, B. (1988). Altered skin permeation of a highly lipophilic molecule: tetrahydrocannabinol. *Int. J. Pharm*., *43*, 17–22.

Trotta, M. (1999). Influence of phase transformation on indomethacin release from microemulsions. *J. Controlled Rel*., *60*, 399–405.

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.

Trotta, M., Ugazio, E., Peira, E., & Pulitano, C. (2003). Influence of ion pairing on topical delivery of retinoic acid from microemulsions. *J. Control. Rel*., *86*, 315–321.

Walters, K. A., Brain, K. R., Howes, D., James, V. J., Kraus, A. L., Teetsel, N. M., Toulon, M., Watkinson, A. C., & Gettings, S. D. (1997). Percutaneous penetration of octyl salicylate from representative sunscreen formulations thorugh human skin in vitro. *Food Chem. Toxicol*., *35*, 1219–1225.

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