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The effect of internal structure of selected water–Tween 40®–Imwitor 308®–IPM microemulsions on ketoprofene release

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Abstract

Microemulsions are a promising vehicle for administrating drugs. In order to lay the basis for predicting drug release under in vivo conditions, where the microemulsion composition is continuously varying, we have studied the release of ketoprofene as a model drug, from microemulsions on a dilution line containing, initially, 20 wt.% of isopropyl miristate (IPM) and 80 wt.% of the surfactant (Tween 40®)/co-surfactant (Imwitor 308®), 1:1 wt.% mixture. Mixture compositions corresponding to the different types and structure of microemulsion were identified by measuring density, surface tension, electric conductivity, pH and differential scanning calorimetry. Ketoprofene release was then measured for each type and structure. The main factor influencing ketoprofene release was shown to be the strength of the interactions between microemulsion components. Strong interactions prevented rapid ketoprofene release in the water-in oil region, although the release was not dependent on the degree of percolation. Release kinetics in all cases follow zero order kinetics, indicating that the release rate is dependent on the diffusion of ketoprofene inside the microemulsion carrier. Combining different methods to obtain the physical and structural properties of microemulsions can be thus used to predict the release of ketoprofen from a microemulsion.

Keywords: Microemulsions; Structure characterisation; Drug release; Ketoprofene

1. Introduction

Colloidal drug delivery systems are important as a means of improving the bioavailability of drugs. Microemulsions are dispersions of oil and water stabilized with a surface active film composed of surfactant and cosurfactant, and are of special interest in this context because of their spontaneous formation, thermodynamic stability and optical transparency (Tenjarla, 1999; Bagwe et al., 2001).

In contrast to the easy preparation of microemulsions, however, it is a far from trivial matter to

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characterize their microstructure. Due to the low interfacial tension between oil and water, a wide range of microemulsion structures is possible. At low water content elongated, rod-like micelles are observed, but water in oil (W/O) spherical droplets, as in classical emulsions but smaller, are also present. In the water rich region, O/W droplets are the most frequent form. In microemulsions with more similar contents of water and oil, bicontinuous structures are formed. Droplets begin to interconnect with several "bridges", described as the percolation phenomenon. When large amounts of surfactants are present, lamellar phases are sometimes observed, which substantially increase the viscosity of the microemulsion. Microemulsions are thermodynamically stable, however their microstructure in the bicontinuous region is continuously changing, complicating structure determination. Using a number of different methods however, such as differential scanning calorimetry (DSC), electric conductivity, density and surface tension, it is possible to characterise the internal structure of the microemulsion (Podlogar et al., 2004). Authors also report that DSC enables the state of water in microemulsion systems to be determined (Garti et al., 1996, 2000; Garti, 2001; Schulz, 1998; Erzahi et al., 2001). Information about the phenomenon of percolation in the system can be obtained by measuring transport and volumetric properties (Eicke et al., 1989; Boned et al., 1993; D'Aprano et al., 1993; Camett et al., 1995; Giustini et al., 1996; Meier, 1996; Sheu, 1996; Weigert et al., 1997; Testard and Zemb, 2000). We showed (Podlogar et al., 2004) that, by comparing these experimental methods it is possible to determine the type and internal structure of the microemulsion, although it is best if we compare results from different samples relatively.

When a microemulsion is introduced into a physiological environment it sooner or later becomes diluted with aqueous medium, resulting in changes in the structure of the microemulsion. It is therefore reasonable to characterise microemulsion samples on the same dilution line. This is most useful if the microemulsion is intended for peroral use. If a microemulsion is intended for topical use, dilution is lower, however, determining the microstructure could enable the release rate of a drug to be predicted. The variety of possible structures means that microemulsions would be expected to release a drug at different rates. In O/W microemulsion, hydrophobic drugs, solubilized mainly in the oil droplets, exhibit hindered diffusion and are therefore released rather slowly. The diffusion of water-soluble drugs, on the other hand, is less restrained. The reverse behaviour is expected in W/O microemulsions. However, diffusion also depends strongly on the oil/water partitioning of the drug and on the pH of the water phase. If pH of the water phase lowers the partitioning coefficient, hydrophobic drugs could be released rapidly from O/W microemulsions. Therefore, the relation between composition, internal microstructure and pH of the water phase of the microemulsion is essential to predict drug release rate from microemulsions.

In order to lay the basis for predicting drug release under in vivo conditions, where the microemulsion composition is continuously varying, we have studied the release of ketoprofene from microemulsions of various compositions on a dilution line with constant ratio of surfactant mixture and IPM to 4:1, whose structures have been determined by physical techniques. Correlations have then been sought between structure and drug release.

2. Materials and methods

2.1. Materials

Isopropyl myristate (IPM) was obtained from Fluka Chemie GmbH, Switzerland, and was used as the lipophilic phase. Tween 40® (TW40)—polyoxyethylene (20) sorbitan monopalmitate (Fluka chemie GmbH, Switzerland) was used as surfactant and Imwitor® 308 (IMW)—glyceryl caprylate (Condea Chemie GmbH, Germany) as cosurfactant. Twice distilled water was used as the hydrophilic phase. Ketoprofene was obtained from Lek d.d., Slovenia.

2.2. Methods

2.2.1. Preparation of the microemulsion carrier system

The surfactant and cosurfactant were blended in a 1:1 mass ratio to give a surfactant mixture. A stock solution was prepared comprising 80 wt.% of this mixture and 20 wt.% of IPM. The appropriate amount of water was then added to obtain the desired microemulsion composition. Components were blended for 5 min at room temperature ($22 \pm 2\,^{\circ}C$)

Table 1
Compositions of the microemulsion samples along the dilution line (shown in Fig. 1)

	Water (wt.%)	IPM (wt.%)	TW40 + IMW
(a) Microemulsions used for the density, electric conductivity, surface tension and DSC measurements			
0	0	19.98	80.02
1	6.33	18.73	74.93
2	9.47	18.10	72.42
3	14.62	17.07	68.30
4	19.90	16.02	64.08
5	24.88	15.02	60.10
6	30.84	13.83	55.32
7	35.06	12.99	51.95
8	40.00	12.00	48.00
9	44.56	11.09	44.35
10	50.52	9.89	39.58
11	60.05	7.99	31.96
12	69.95	6.01	24.04
(b) Microemulsions used in the drug release study			
I	10.00	18.00	72.00
II	22.03	15.60	62.37
III	31.96	13.61	54.43
IV	49.34	9.91	39.55
V	60.05	7.99	31.96
VI	69.95	6.01	24.04

using a magnetic stirrer. All samples were stable over 6 months, remaining clear and transparent.

The compositions of the microemulsions are given in Table 1, and the corresponding dilution curve is drawn on a pseudoternary diagram (Fig. 1).

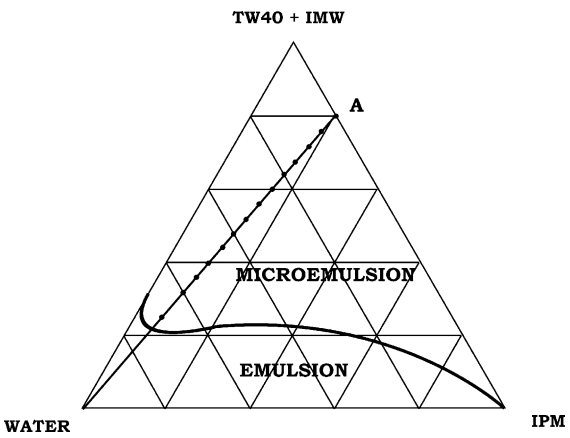

Fig. 1. The pseudo-ternary phase diagram for the mixture isopropyl myristate–Tween 40®–Imwitor 308®–water. A: the investigated dilution line.

Into microemulsion samples, selected for drug release study, ketoprofene was added to already prepared microemulsions to give 1.2 wt.% concentration of the drug, and mixed using a magnetic stirrer for 15 min at room temperature ($22 \pm 2\,^{\circ}C$).

2.2.2. Density

Densities were determined with a Paar digital precision density meter DMA 60 and an external measuring cell DMA 602 (Anton Paar, Austria). Temperature was controlled at $25.00 \pm 0.01\,^{\circ}C$. The accuracy of density measurements was within $\pm 5 \times 10^{-6}\,kg\,dm^{-3}$.

2.2.3. Surface tension

Surface tension was measured at $25 \pm 0.5\,^{\circ}C$ with a Kruss processor tensiometer K21 (Kruss GmbH, Germany) using Wilhelmy's plate method. A square platinum plate was cleaned, rinsed with twice distilled water and heated in a reductive flame to purge all impurities. This cleaning procedure was repeated before every measurement. During the measurement the plate is dipped into the liquid, requiring about 30 ml sample. The tensiometer measures the pulling force of the liquid on the plate, which, with known plate size, yields the surface tension.

2.2.4. Electric conductivity

Conductance was measured using an Iskra conductivity meter MA 5964 (Iskra, Slovenia) with a home-made conductivity cell with cell constant of $0.7265\,cm^{-1}$.

Conductivity and surface tension measurements require large amount of samples and for this reason they were carried out during titration of the starting mixtures of surfactant, cosurfactant and IPM with water.

2.2.5. Differential scanning calorimetry

DSC measurements were performed with a differential scanning calorimeter DSC-4 (Perkin-Elmer, USA). Nitrogen with a flow of 20 ml/min was used as purge gas. Approximately 5–15 mg of sample was weighed precisely into a small aluminium pan and quickly sealed hermetically to prevent water evaporation. The empty sealed pan was used as reference. Samples were cooled from 30 to $-60\,^{\circ}C$ (cooling rate 10 K/min).

2.2.6. Measurement of ketoprofene release

Ketoprofen release through a hydrophilic cellulose acetate membrane was determined with a Franz diffusion cell (Hanson research, Chatsworth, USA) at 25 °C. The cell held 7 ml of acceptor medium (phosphate buffer pH 7.4), and 0.3 g microemulsion on the donor side; the surface area between acceptor and donor compartments was 1.18 cm^2. After introduction of microemulsions containing 1.2 wt.% ketoprofene, samples were taken from the acceptor medium at 0.5, 1, 1.5, 2, 3, 4, 5, 6 and 8 h intervals, and assayed for ketoprofen content at 260 nm (UV spectrophotometer 8453, Hewlett Packard, Waldbronn, Germany). This experiment was carried out in triplicate. Results are reported as arithmetic means. Comparisons were performed by Student's *t*-test. Significance was tested at the 0.05 level of probability.

Drug release was determined by two parameters: the amount of released drug after 8 h and the release rate of the drug expressed as the slope of the linear regression line. We also determined the order of the release kinetics (zero order, first order or Higuchi) by comparing Pearson coefficients of the linear regression lines for the different rate equations. Logarithm of amount released was plotted against time for first order and against square root of time for Higuchi kinetics. The accepted order of kinetics is the one that yields a linear function with Pearson coefficient closest to 1.

pH of microemulsion with and without ketoprofene was determined at 25 °C using the combined pH electrode (METTLER TOLEDO Inlab® 423) and pH meter ISKRA MA 5740.

3. Results and discussion

In our previous work the disadvantages of microemulsions for pharmaceutical use that contain large amounts of surfactants was discussed shortly (Podlogar et al., 2004). However, often there is no other way to obtain stable microemulsion systems, especially when a broad quantitative composition range should be under investigation. In this study a dilution line was chosen starting with 20 wt.% of isopropyl miristate (IPM) and 80 wt.% of the 1:1 surfactant (Tween 40®)/co-surfactant (Imwitor 308®) mixture. The concentration of surfactant ranged from 80 wt.% Tween/Imwitor to ∼24 wt.% (Table 1). While the ratio of the surfactant mixture to oil (IPM) was kept constant at 4:1, the concentration of IPM was reduced by dilution from 20 to 6 wt.%.

Due to the strong amphiphilic nature of the Tween/Imwitor mixture, the investigated systems are expected to form a wide variety of different nanostructures dispersed in the continuous phase, which is either oil (IPM) or water, depending on the relative concentrations.

3.1. Density and surface tension

Values of density and surface tension are plotted against weight ratio of water (Fig. 2).

The density increases monotonically up to ∼15 wt.% water, after which it remains constant or decreases slightly. Given that the densities of water and of the starting solution of the surfactant mixture in IPM are 0.997047 and 1.003446 g cm^{-3}, and assuming ideal additivity of volumes, we can calculate the excess volume, $V^E = V_{exp} - V_{id}$, as a function of water content (see inset Fig. 2). It shows that volumes are in fact not additive. Considerable contraction of volume occurs (V^E decreases) up to ∼15 wt.% water. At higher water content V^E changes little, suggesting that attractive interactions are similar in that region. It was not possible to determine the density above 35 wt.% water because of the higher viscosity of the sample.

The surface tension decreases linearly over the same range of water content, but two breaks (at 15 and

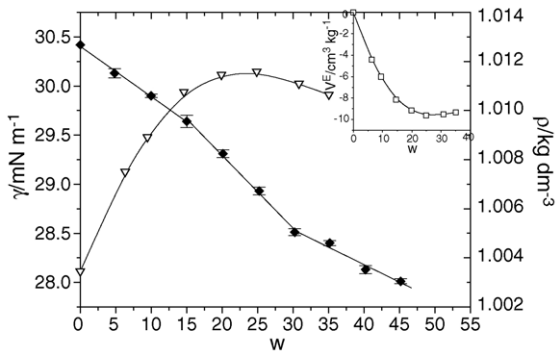

Fig. 2. The dependence of surface tension (♦) and density (▽) on the water weight ratio (w) in water–Tween 40®–Imwitor 308®–isopropyl myristate microemulsions. Inset: the excess volume, V^E, as a function of weight ratio.

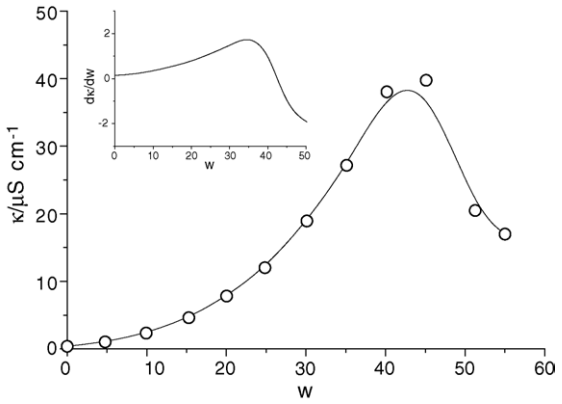

Fig. 3. Electric conductivity (O) as a function of the water wt.% (w) in the water–Tween 40®–Imwitor 308®–isopropyl myristate microemulsions. Inset: The first derivative of the electric conductivity.

30 wt.% water) suggest that structure changes occur at these compositions.

The results coincide well with the electric conductivity and DSC measurements, as discussed further below.

3.2. Electric conductivity

Electric conductivity, presented in Fig. 3 as a function of water content, varies according to a bell-shaped curve. A similar dependence was observed for microemulsions with fixed surfactant concentration with the percolation transition (Borkovec et al., 1988; Giustini et al., 1996), indicating that the system changes to an interconnected bicontinuous structure.

The conductivity of the IPM and surfactant mixture was around 0.4 μS cm^{-1}. With the addition of water the conductance increased monotonically up to ∼15%, reflecting the higher conductivity of water compared to that of the IPM and surfactant mixture.

When more water is added an increase in conductivity is observed, which is typical of the clustering of the droplets at the percolation threshold (Boned et al., 1993; Giustini et al., 1996; Gradzielski and Hoffman, 1999; Podlogar et al., 2004). The percolation threshold can be determined from the plot ($d\kappa/dw$), as a function of the water weight fraction, w (Fig. 3 inset). The maximum in the first derivative at ∼35 wt.% water in the microemulsion confirms the presence of percolative behaviour in this region (Gradzielski and Hoffman, 1999).

The conductivity of the microemulsions containing more than 50 wt.% water decreased significantly, probably due to the higher viscosity.

3.3. DSC measurements

The state of water in microemulsion system is indicated by the size and position of the peak in the DSC cooling curve that represents the freezing of water (Garti, 2001). Water molecules that interact strongly with surfactants solidify at lower temperatures than those with weaker interactions. The enthalpy of freezing is also different.

In cooling curves of samples with ∼5 and 10 wt.% water (curves 1 and 2 in Fig. 4), the broadest peak appears at approximately −8 °C and indicates the solidification of IPM. The second, narrower peak at approximately −38 °C, probably indicates freezing of the surfactant mixture (Podlogar et al., 2004). No freezing peak of water molecules was observed in samples containing 0–15 wt.% water. A possible explanation is that, due to the large amount of surfactant present in these samples, water interacts strongly, lowering the freezing point to very low temperatures and giving a very low freezing enthalpy, probably below the limit of detection. At 20 wt.% water (Sample 4), a distinct change in the cooling curve is observed. A new peak appears at approximately −48 °C, which, with increasing amounts of water, increases in area and moves towards higher temperatures. It is reasonable to assume that it indicates the freezing of internal or bound water (Podlogar et al., 2004). Since the freezing temperature is very low, the water must be strongly bound or interacting with surfactants. The results parallel those from electric conductivity, surface tension and density measurements. Between 25 and 40 wt.% water the excess volumes are also very similar and could indicate a percolative region.

At more than 40 wt.% water (curves 8–12 in Fig. 4) one large, sharp peak is observed in the temperature range between −19 and −26 °C, indicating the freezing of supercooled water with less interaction with other molecules. Our assumption was confirmed with reference measurement of pure double distilled water, where a similar peak at approximately −19 °C was also observed. From the DSC measurements, it

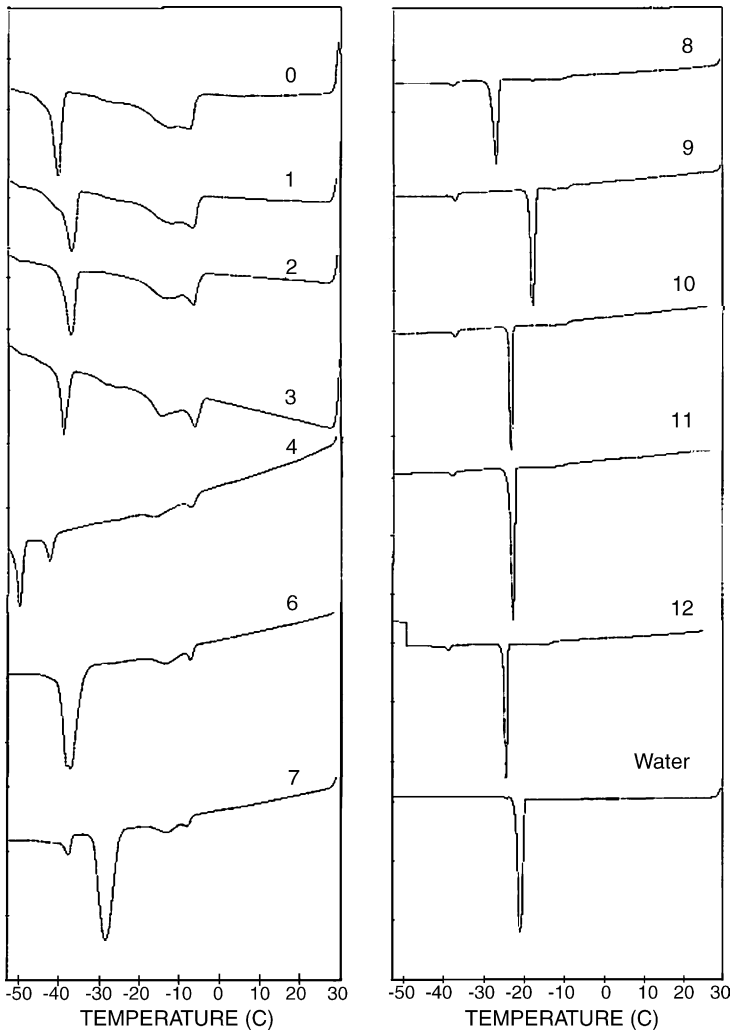

Fig. 4. DSC cooling curves of the microemulsions. Numbers next to the curves denote the sample composition, given in Table 1a. The cooling curve for pure water is also shown.

can be concluded that the water in systems containing more than 40 wt.% is in the outer phase, i.e. the microemulsions are O/W.

3.4. Selecting samples for ketoprofene release studies

To summarize the above results, the following types of structure are observed: W/O type (10% water), start of the percolation phenomenon (22%), bicontinuous phases (32%), O/W type (50%) and gel-like microemulsion (60 and 70%) (Table 1b). Into each of these samples 1.2 wt.% of ketoprofene was dissolved.

Ketoprofene is a non-steroidal anti-inflammtory drug. Its structure contains a large lipophilic and a small hydrophilic domain (–COOH). It has good permeability and poor solubility in water (Lennemäs et al., 1996) although, since it is weak acid, its solubility increases at higher pH. With its apolar and polar domains it could act as a cosurfactant, raising the possibility that, on solubilization, it will not only remain in the oil phase but also be incorporated in the surfactant film, causing the microemulsion structure to change.

Although some microemulsions could solubilize more than 10 wt.% of ketoprofen and remain transparent, 1.2 wt.% concentration was chosen to minimize any effect of ketoprofene on the microemulsion structure. This concentration still allows a measurable response and thus reproducible measurement of ketoprofene release.

3.5. Influence of ketoprofen on the microemulsion structure

Samples containing 1.2 wt.% of ketoprofen were analysed by electric conductivity, pH and DSC measurement to observe possible changes in the microemulsion structure and/or properties.

Adding ketoprofen does not greatly change the electric conductivity of samples containing up to 32 wt.% water, however, at higher water content, the difference becomes more pronounced (Fig. 5). This is the result of the lower viscosity (not presented here) of samples containing ketoprofene in the water rich region compared to those without the drug. In the absence of ketoprofene, samples with more than 50 wt.% water are more viscous due to strong attractive forces (Podlogar et al., 2004). Ketoprofen, with its amphiphilic nature, prevents formation of such strong interactions; the viscosity is lower which yields higher conductivity. We can conclude that, regarding electric conductivity, ketoprofen does not alter microemulsion structure in samples containing up to 40 wt.% water, but it prevents formation of a gel-like structure, which was formed in that region prior ketoprofene addition.

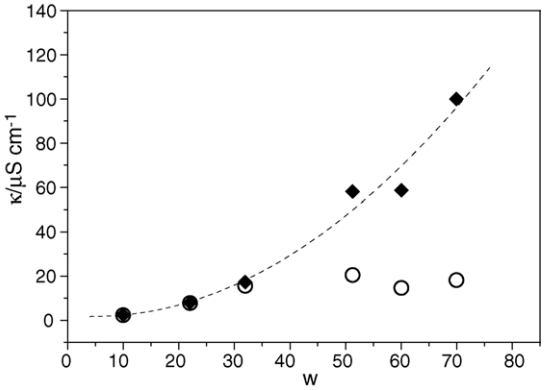

Fig. 5. Electric conductivity of samples without (O) and with (♦) added ketoprofene.

Similar conclusions can be reached from the DSC curves (Fig. 6). Addition of ketoprofene to microemulsions with up to 30 wt.% water does not greatly alter the DSC curve (Sample III in Fig. 6), but a change is observed in samples containing more than ∼50 wt.% water. Such behaviour represents Sample VI with

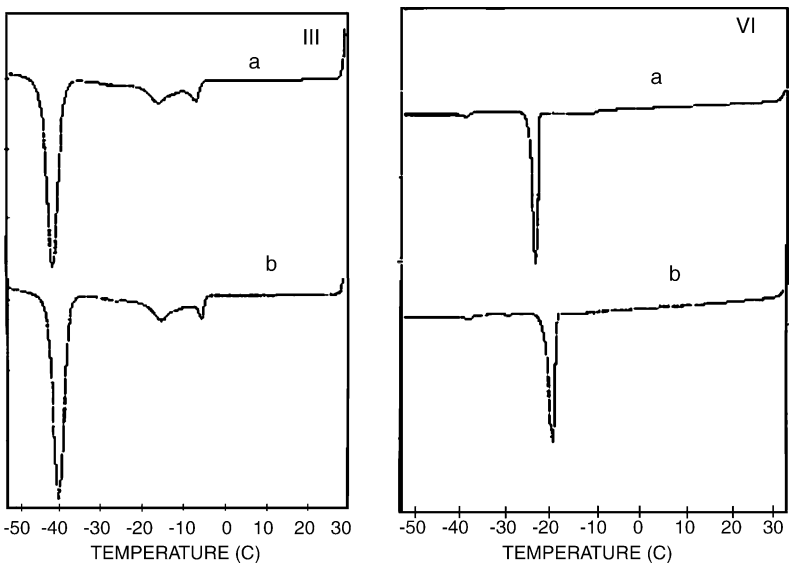

Fig. 6. DSC cooling curves of Samples III and VI without (a) and with (b) added ketoprofene.

Table 2
Ketoprofene release rates, Pearson coefficients and pH at 25 °C for different microemulsion compositions (see Table 1b assuming zero order kinetics

Sample	Drug release rate (mg/h)	Pearson coefficient	pH	
			Blank microemulsion	Microemulsion with ketoprofene
I	0.0450	0.9955	4.54	4.26
II	0.0498	0.9970	4.38	3.69
III	0.0493	0.9880	4.07	3.65
IV	0.0598	0.9967	3.93	3.25
V	0.0703	0.9970	3.68	2.93
VI	0.0752	0.9829	3.56	2.80

70 wt.% of water (Fig. 6). In this case we observe that the freezing enthalpy, associated with the freezing of water in the outer phase, changes. Also, the peak is moved towards higher temperatures, indicating that interactions between water molecules and surfactants are weaker. This supports the conclusions from electric conductivity and confirms that ketoprofene prevents formation of the strong interactions that are necessary for gel formation.

Adding ketoprofene, a weak acid, lowers the pH of the microemulsion (Table 2). The same amount of added drug causes different reductions of the pH from 0.28 in the sample with 10 wt.% water up to an almost constant value of 0.75 (except at 50 wt.%) for samples with more than 30 wt.% water, indicating the crucial influence of the state of water in different samples.

3.6. Ketoprofene release

In vitro release studies with an artificial hydrophilic membrane can provide information about the diffusion of the drug, which depends on vehicle internal structure, diffusion of the drug inside the carrier system and pH of the water phase (Jurkovič et al., 2003; Kreilgaard, 2002). Any information regarding in vivo permeability of the drug is not obtained. Ketoprofene release through an artificial membrane was characterized by two parameters: the amount of drug released after 8 h and the rate of release of the drug. During the release experiment, microemulsions remained visually clear and transparent. There was no visual indication that water from acceptor compartment penetrated into microemulsion what could result in its inversion into coarse emulsion.

Comparing the amounts of drug released after 8 h (Fig. 7) the slowest release was observed from W/O microemulsions (Sample I—Table 1b); in the bicontinuous region (Samples II and III) the amount released is significantly higher ($p = 0.0036$). Sample II—at the percolation threshold—and Sample III—where percolation is more pronounced—both yield the same result indicating that amount of released drug after 8 h is not dependent on the degree of percolation phenomenon. It is possible that percolation offers somewhat greater ketoprofene mobility than W/O microemulsion (Sample I), however the diffusion of a small amount of ketoprofene through percolation channels (Samples II and III) is not dependent on the size of the channel. The excess volume curve (inset Fig. 2) shows that Samples II and III (22 and 32 wt.% water) have similar excess volumes. It is evident that, in the percolative region, samples with similar excess volumes exhibit similar ketoprofene release after 8 h. The sur-

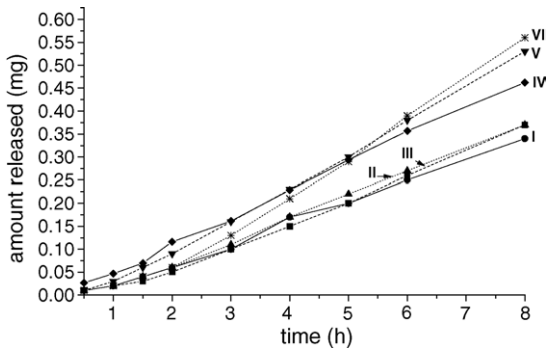

Fig. 7. Release profiles of microemulsions of different composition. Numbers next to the curves denote the sample composition, given in Table 1b.

prising similarity between bicontinuous and W/O types of microemulsions can be explained by assuming that release depends more on the surfactant film, where the ketoprofene acts as a co-surfactant and is incorporated in the interfacial film, than on the properties of the environment.

A pronounced change in the amount of drug released is observed when the microemulsion is in the O/W form (Samples IV–VI). Ketoprofene, with its amphiphilic nature, has already been seen to prevent formation of strong interactions in this region. The viscosity is lower, suggesting the presence of more free water in the microemulsion, as was also indicated by the considerably lower pH of samples containing ketoprofene.

Release rates are presented in Table 2. For all samples, a zero order kinetic mechanism gives the best fit, although a very small deviation from zero order is observed in some cases. Thus, ketoprofene release rate from our microemulsions is dependent mostly on the diffusion of ketoprofene inside the microemulsion carrier.

The amount and rate of ketoprofene release differs significantly between microemulsion carrier systems with different internal microstructures in all cases except between Samples II and III (both in the percolative region) ($p = 0.74$) for the reasons explained above. Samples V and VI also release the same amount of drug after 8 h ($p = 0.14$), although the rate is significantly different ($p = 0.047$), implying different diffusion kinetics.

From pH measurements of microemulsions (Table 2) release rate would be expected to be slower in a water rich region, because lower pH of microemulsion with consequently lower solubility of ketoprofene slows down its diffusion into water phase. However, the opposite effect was observed. Acceptor medium is buffer with much larger volume than the sample, so it is probable that the pH is constant during the release experiment and it does not influence the release rate changes. It appears that strong interactions between ketoprofene, oil and surfactants are the key factors that prevent faster ketoprofene release in W/O microemulsions.

Stronger interactions between microemulsion components in W/O microemulsions as well as in the bicontinuous phase, lead to slower ketoprofene release although, in the case of dilution in physiological medium, pH and microemulsion structure both change, which would lead to different ketoprofene release.

4. Conclusion

At the selected dilution line we can conclude that a microemulsion containing less than ∼20 wt.% water is expected to be oil continuous; however, surfactants, because of their large amount, are also present in the continuous phase. A microemulsion containing between 20 and 40 wt.% water will be water as well as oil continuous–bicontinuous microemulsions. Finally, a microemulsion containing more than 40 wt.% water is expected to be O/W. When more than 45 wt.% water is present in the system the presence of strong interparticle interactions between droplets leads to a gel-like structure. The hydrophilic chains of non-ionic surfactant are expected to be strongly hydrated and connected by hydrogen bonds, resulting in strong interactions. The presence of ketoprofen in microemulsions prevents the formation of such strong interactions.

We have shown that release of ketoprofene can be predicted to a certain extent, using a combination of several methods for physical characterisation of microemulsions. Samples that were identified as having different structures were shown, with one exception (percolation range), to have different release profiles. The release kinetics were in all cases zero order, meaning that the release rate is dependent on diffusion of ketoprofene inside the microemulsion carrier. Strong interactions between ketoprofene, oil and surfactants prevent faster ketoprofene release in the W/O region. Ketoprofene (1.2 wt.%) does not alter the microemulsion system significantly, however its presence prevents the formation of stronger interactions and formation of gel-like structure in the water rich region.

The characterisation of the microstructure of microemulsions by a group of experimental methods is seen to allow prediction of ketoprofene release from microemulsion as well as enabling an insight into how a microemulsion might change its structure and therefore its ability to release ketoprofene upon entering a physiological environment.

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