

PROBING THE MICROSTRUCTURE OF LIQUID CRYSTALLINE SURFACTANT SYSTEMS; A PHYSICOCHEMICAL STUDY USING RHEOMETRY, DTA AND ^{17}O NMR

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Mixtures of Brij 96 (decaethylene oxide oleyl ether) and water form liquid crystalline systems (creams) which have a potential as dosage forms for controlled dermal and transdermal drug delivery. By changing the water-surfactant mixing ratio in these systems, lamellar, viscous isotropic or hexagonal liquid crystalline phases can be obtained. First, a number of liquid crystalline creams were characterized using rheometry. Going from a lamellar cream (low water content) to a hexagonal (high water content) one, the macroscopic viscosity strongly increased. In Brij 96-water creams, the poly(ethylene oxide) (PEO) chains of the surfactant molecules and the water form a continuous hydrophilic domain, the microstructure of which will be important for the diffusion of drugs through the creams. The hydrophilic domains in the liquid crystalline creams were investigated using ^{17}O nuclear magnetic relaxation and differential thermal analysis and compared with those of PEO-water solutions. From these studies the conclusions were drawn that (i) the hydrophilic domains may be regarded as PEO solutions in water, and that (ii) the cream structure has no detectable influence on the properties of the microstructure of the hydrophilic domains. In the most concentrated creams and PEO solutions studied, having a water-EO ratio of 1.5, an 8-fold retardation of the rotational mobility of the water molecules was observed using ^{17}O nuclear magnetic relaxation.

INTRODUCTION

The structures of liquid crystalline systems consisting of mixtures of the nonionic surfactant Brij 96 (decaethylene oxide oleyl ether) and water have been studied previously [1,2]. Depending on the Brij 96-water mixing ratio,

these systems can have various liquid crystalline phases: lamellar (L), hexagonal (H) or viscous isotropic (VI). Such mixtures of Brij 96 and water can be considered as simplified versions of creams (they contain water and surfactant but there is no additional oil component present); henceforth they will be referred to as creams. In the literature these systems are also referred to as lyotropic mesophases or lyotropic liquid crystalline phases [1,3], polyglycol ether

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gels [4], transparent hydrogels [5], or "Transparente Tensidele" [6].

The application of the creams as dosage forms in dermal and transdermal drug delivery have been discussed by Boddé et al. [7] and by Tiemessen et al. [2].

While liquid crystalline phases have been investigated thoroughly, only a few studies have been performed to evaluate their influence on drug release from the liquid crystalline creams (e.g. by Müller-Goyman and Frank [8]). In a previous report, in which the release of benzocaine from Brij 96-water creams was studied, it was shown that the diffusion coefficient of benzocaine increased gradually with increasing water content in lamellar and hexagonal creams [2]. In fact, the close relationship between structure and benzocaine release found with these systems led to the suggestion that the hydrophilic channels in the creams are the major transport pathways for this drug. However, in the case of the viscous isotropic structure, a relatively high (ca. 50% increase) benzocaine diffusivity was found, most likely related to the open network character of the VI phase. All creams studied contain a continuous hydrophilic domain on the one hand, which contains the water and the polyethylene oxide (PEO) surfactant chains, and hydrophobic domains on the other. It could be expected that very lipophilic drugs might diffuse mainly through the hydrophobic domains, while amphiphilic drugs might diffuse mainly along the interfaces between the hydrophilic and hydrophobic domains. However, most drugs are likely to be able to diffuse through the hydrophilic domains, since they are solubilized by the PEO chains of the surfactant molecules. Furthermore, the hydrophilic domains form a continuous domain which is in all cases important for drug diffusion in the creams, regardless of the cream structure.

The nature of the hydrophilic domains will have a strong influence on the diffusion of a drug. Boddé et al. [9] suggested that only the unbound water molecules [> 2 per ethylene ox-

ide (EO) unit] contribute to the drug permeation of the hydrophilic drug nicotinamide in crystalline creams. Graham et al. [10], however, concluded from studies of caffeine release from swollen PEO hydrogels that "if tightly bound water is present it does not evidence itself by any effect on the diffusion characteristics of caffeine". Considering the nature of the hydrophilic domain, two questions arise. (a) Do the hydrophilic domains contain two types of water: highly ordered water bound to the PEO chains and free water, or do they contain a homogeneous mixture of water and PEO? (b) Is there any influence of the cream structure on the nature of hydrophilic domains?

In the literature on PEO alkyl ether-water mixtures, the hydrophilic domains are often considered to consist of hydrated polar headgroups and (layers of) free water molecules [8,11]. Physicochemical studies in which the self-diffusion of water was determined in aqueous solutions of $C_{12}EO_5$, $C_{12}EO_8$ and PEO showed that the degree of hydration of the PEO decreased with increasing temperature and increasing concentration, but was independent of the particular system studied [12]. The hydration numbers (the number of water molecules "bound" to one EO unit) obtained in different studies depend on the techniques and the definition used.

Breen et al. [13] concluded from ^{17}O nuclear magnetic relaxation studies on diluted PEO solutions that there may be a small but distinct preferential orientation of water molecules in the proximity of the PEO. The correlation time, describing the rotational diffusion of a water molecule, was estimated to be increased by a factor of 2 to 5 (4 to 10 ps, depending on the hydration number used in the calculations) compared to values obtained in pure water.

Acknowledging the fact that the microstructure of the hydrophilic domains may be of consequence for drug transport, this study aims at probing the hydrophilic domains of liquid crystalline creams, using three techniques: rheo-

metry, differential thermal analysis (DTA), and ^{17}O NMR. Creams with lamellar, viscous isotropic and hexagonal liquid crystalline structures were characterized rheologically to illustrate the strong influence of the liquid crystalline structure and cream composition on its rheological behaviour, and to probe correlations between the properties of the hydrophilic domains and the macroscopic viscosity. DTA was used to find out whether the water in the hydrophilic domains and that in PEO solutions have a similar freezing behaviour. ^{17}O nuclear magnetic relaxation studies were performed to test whether the conclusions of Breen et al. [13] can be extended (i) to more concentrated PEO solutions and (ii) to the hydrophilic domains in Brij 96–water creams. Using the latter two techniques, the influence of the cream structures on the behaviour of water was characterized by comparing creams and PEO solutions.

MATERIALS AND METHODS

PEG 400 (PEO_9) was obtained from Brocacef (Maarsse, The Netherlands). Brij 96, decethylene oxide oleyl ether, was a gift from Atlas Chemie (Essen, F.R.G.). Two batches of the surfactant Brij 96 used were investigated by ^1H NMR to check the average number of ethylene oxide units per molecule [2]. The two batches appeared to have a lower EO number than specified: 8.5 ± 0.2 (batch A 6910) and 9.3 ± 0.2 (batch 596606). In the following, the two batches will be referred to as Brij 96 (EO8.5) and Brij 96 (EO9.3), respectively.

Depending on the batch of the surfactant used, the creams with water contents of ca. 35% may exhibit either a mixture of lamellar and hexagonal structures [Brij 96 (EO8.5)] or a viscous isotropic liquid crystalline structure [Brij 96 (EO9.3)]. Reagent-grade water was produced by a Milli-Q filtration system; the final resistivity of the water was greater than $10 \text{ M}\Omega \cdot \text{cm}$. For preparation of the creams, Brij 96 and water were weighed into glass vials, sealed,

heated to 80°C , homogenized by shaking and cooled to room temperature. Water which had evaporated during the preparation procedure was not replaced and the final water content was determined gravimetrically, the final weight fractions being B (Brij 96) and W (water). The water weight fraction of the creams ranged from 0.20 up to 0.70. The water weight fractions in the hydrophilic cream domains, f_w , were calculated as follows:

$$f_w = W / (W + \mu B) \quad (1)$$

where μ is the (average) molecular weight fraction of the polyoxyethylene part of the surfactant molecules. $\mu = 0.630$ for Brij 96 (EO9.3) and $\mu = 0.609$ for Brij 96 (EO8.5).

Rheometry

Rheological measurements were carried out on a Carri-Med Controlled Stress Rheometer (Carri-Med Ltd., Dorking, U.K.) at 21°C , using a cone-and-plate system. The samples were transferred to the rheometer with a spatula, taking care to disturb the sample as little as possible. In some cases, the apparent viscosity was calculated from the ratio of the shear stress and the shear rate.

Differential thermal analysis (DTA)

DTA measurements were carried out using a Mettler DSC30 (TA 3000 system, Greifensee, Switzerland). Only cooling experiments were performed, with a cooling rate of $5^\circ\text{C}/\text{min}$.

Nuclear magnetic relaxation

Water isotopically enriched in ^{17}O was obtained from the Monsanto Research Corporation, Miamisburg, FL: it contained 9.9% ^{16}O , 51.1% ^{17}O , and 39.0% ^{18}O . Each sample spiked with isotopically enriched water contained less than 0.0015 mole fraction of ^{17}O . It has been verified that oxygen isotope effects on the ^{17}O relaxation rate are negligible [14]. The relax-

ation rates were measured on three different spectrometers: a home-built spectrometer equipped with a 2.1 T electromagnet (Bruker), a modified Bruker-SXP spectrometer with a 6.3 T superconducting magnet (Oxford Instruments), and a Bruker MSL-400 spectrometer with a 9.3 T superconducting magnet. The temperature was controlled at 25°C by either a fluid (Fluorinert FC 43, 3M Co.) or a gas thermostat (Bruker VT 1000).

Longitudinal relaxation rates were obtained at least in duplicate by the inversion recovery method with a reproducibility of 2%. Free induction decays were accumulated while the relative phase of the π and $\pi/2$ pulses was alternated [15]. The relaxation delay was 100 ms, far exceeding 5 times the characteristic relaxation times. The viscous isotropic cream structures showed a single resonance. In the cases of the lamellar and hexagonal cream structures, a quadrupole splitting of ca. 70 ppm was observed. The relaxation was observed to be a single exponential. No field dependence and no difference in relaxation rate between the different magnetic transitions were observed.

RESULTS AND DISCUSSION

Rheology

One of the main reasons to determine the rheology of topically applied semisolids is to monitor the effects of the viscosity of the vehicle on drug release from the vehicle. According to the Stokes-Einstein equation, the diffusivity of a drug is inversely proportional to the viscosity of the medium in which it diffuses. In a review on the rheology of dermatological vehicles, however, Barry [16] concluded that in practice there is often a lack of correlation between rheological parameters and drug release rates or bioavailability. It was concluded that the absence of this correlation may be explained by the fact that the rheological measurements (bulk or macroviscosity) do not correspond

with the conditions which exist in the environment surrounding the diffusing molecule (microviscosity). In this study three creams were characterized rheologically in order to evaluate the influence of macroscopical viscosity on the hydrophilic domains, the true environment of the diffusing drug molecule.

Figure 1 shows the rheograms of a lamellar, viscous isotropic and hexagonal Brij 96 (EO9.3)-water cream obtained with the controlled stress rheometer. The rheogram of the lamellar 80/20 Brij 96-water cream was obtained in the following way: the shear stress was increased for 1 min, held for 1 min and decreased for 1 min. The cream shows a pseudoplastic flow behaviour. The "up curve" coincides with the "down curve", indicating an absence of thixotropy. The apparent viscosity under the experimental conditions ranges between 0.5 and 1.4 Pa·s. This flow behaviour may be explained by the relatively easy alignment of the lamellae in the direction of the flow. The lamellae are extended layers containing the lipophilic chains of the surfactant molecules, and are separated by the hydrophilic domains which contain the hydrophilic chains of the surfactant molecules and the water.

The viscous isotropic cream, however, showed a plastic flow behaviour (Fig. 1A) when the stress was increased during 1 min. A yield stress of ca. 750 Pa was observed. The "peak hold" and "down curves" could not be obtained because of the slippage of the cone. The yield stress is required to break down the well ordered three-dimensional viscous isotropic structure, which is not well understood yet but is supposed to be continuous in three axial directions with respect to both the hydrophilic and the hydrophobic domains [3].

In the case of the hexagonal cream, the rheogram was taken as follows: the shear stress was increased for 3 min, held for 1 min and decreased for 3 min. A yield stress of ca. 200 Pa was observed. The apparent viscosity decreased in the "up curve", while during the 1 min in which the shear stress was kept constant

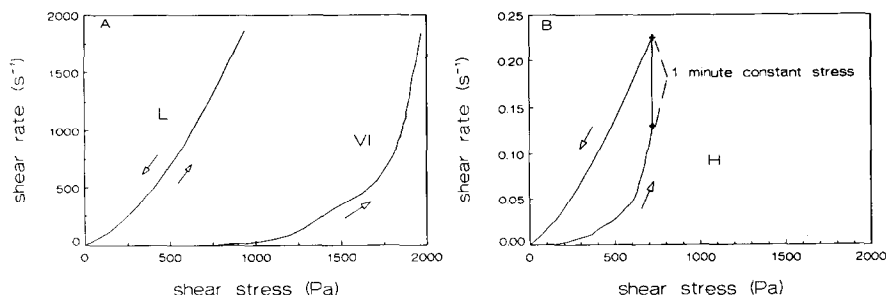


Fig. 1. Rheograms of three creams having the following composition and structure: (A) a lamellar 80/20 Brij 96 (EO9.3)-water cream, a viscous isotropic 65/35 Brij 96 (EO9.3)-water cream and (B) a hexagonal 50/50 Brij 96 (EO9.3)-water cream. The experimental conditions under which the rheograms were obtained are given in the text.

the apparent viscosity decreased from 5500 to 3200 Pa·s. The observed high apparent viscosity (higher than 3200 Pa·s throughout this experiment) must be due to the very low mobility of the rod-shaped aggregates inside the hexagonal structures of the creams. The creams are composed of cylindrical surfactant aggregates arranged in a hexagonal array. The hydrophobic surfactant moieties are on the inside of the cylinders, while the hydrophilic parts are on the outside and contribute, together with the water, to the continuous hydrophilic phase. This is the so-called “normal” hexagonal or H₁ phase. Under the influence of the applied stress, the cylindrical aggregates are aligned to some extent, leading to a decrease in apparent viscosity. When the applied stress is decreased the reconstitution of the original structure, if it takes place, will only be slow, and therefore the viscosity will remain at a lower level for some time (thixotropy).

The rheograms underscore the large differences in rheological behaviour previously reported by Nürnberg and Pohler [17]. The most remarkable feature of these surfactant-water systems is the observed increase in viscosity when the surfactant solution is diluted with water, and the lamellar structure is transformed (using this Brij 96 batch, via a viscous isotropic structure) to a hexagonal structure. Most interestingly, the diffusivity of benzocaine in hexagonal creams is higher than in la-

mellar creams, as previously reported [2]. Hence it is obvious that the drug diffusivity is not related to the macroscopic viscosity of the liquid crystalline phases determined experimentally.

Differential thermal analysis (DTA)

Cooling scans have been made of both aqueous PEO (PEG 400) solutions and Brij 96-water creams. Both the position (freezing point) and the surface area (freezing enthalpy) of the water freezing peak have been determined. Figure 2 shows the observed freezing enthalpies as a function of the water weight fraction, f_w , for the PEO solutions and for the hydrophilic domains of the hexagonal Brij 96 (EO8.5)-water creams, calculated according to eqn. (1). The observed freezing points in-

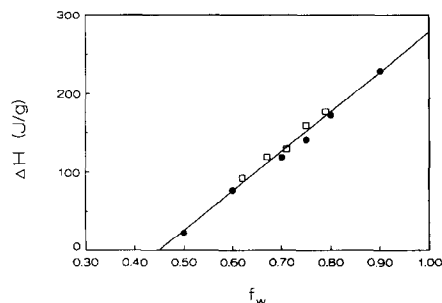


Fig. 2. Enthalpy changes due to freezing of water in (●) PEO(9)-water mixtures and (□) hexagonal Brij 96 (EO8.5)-water creams.

creased with increasing water content, ranging from -45 to -14°C . The observed freezing point depression in the Brij 96–water mixtures was smaller than in the corresponding PEO–water mixtures. The surfactant–water mixtures form hexagonal liquid crystalline phases at ambient temperatures. Upon decreasing the water content, the freezing enthalpy steadily decreased and finally could not be resolved with accuracy, because the freezing point appeared to be too near to the very broad peak caused by the crystallization of the hydrocarbon chains. Below $f_w=0.45$ the water freezing peak vanished. The coincidence of all data points on the linear best fit clearly shows that the freezing behaviour of the water in the PEO solution and in the hydrophilic domains of the Brij 96 (EO8.5)–water mixtures is indistinguishable. The linear least squares fit intersects the composition axis at 0.449. The number of water molecules per EO unit, n , can be calculated from:

$$n = \frac{f_w}{1-f_w} \cdot \frac{M_{\text{EO}}}{M_w} \quad (2)$$

where M_{EO} denotes the molecular weight of the EO unit ($M_{\text{EO}}=44$) and M_w denotes the molecular weight of the water molecule. From the fact that at $f_w=0.449$ the freezing enthalpy becomes zero, it can be calculated, using eqn. (2) and neglecting the terminal hydroxyl group effects, that two (1.99) molecules of water per EO unit do not freeze under the present experimental conditions. The results obtained are in perfect agreement with experimental data obtained by De Vringer et al. [18], who also found a hydration number of 2 in the freezing of PEG 1550–water mixtures. Extrapolation of the linear least squares fit to pure water ($f_w=1$) yields a value of 278 J/g, which is significantly less than the theoretically expected melt enthalpy of pure ice (333.5 J/g). This deviation is caused by supercooling effects. A correction for the supercooling effects using the methods and assumptions described by De Vringer [18] yielded a value of 317 J/g (95% confidence interval 295–

345 J/g), which is in agreement with the theoretical value.

Nuclear magnetic relaxation (NMR)

In heterogeneous systems, the nuclear magnetic relaxation of solvent nuclei (i.e. ^1H , ^2H and ^{17}O) may provide information about the water dynamics [19]. One of the disadvantages of ^1H NMR is that the interpretation of the ^1H relaxation data is complicated, due to the fact that inter- and intra-molecular dipolar interaction contributions to the relaxation rate are difficult to separate. However, the ^2H and ^{17}O nuclei relax completely intramolecularly by the quadrupolar interaction mechanism [14]. Hence the corresponding NMR spin–lattice relaxation rate values are sensitive to the single molecular reorientational motion. The relaxation of these nuclei has been used to study the structure and dynamics of water in a variety of solutions, such as pure water [14,20,21], polyelectrolyte solutions [22], poly(hydroxyethyl methacrylate) hydrogels [23], and polyethylene oxide solutions [13].

As shown by the data, in the Brij 96–water creams the reorientational motion of water occurs on a picosecond time scale. As a consequence, the extreme narrowing condition is fulfilled and the nuclear relaxation rate (R) is directly proportional to the reorientational correlation time t_c [24]:

$$R_O = 3/125 (2\pi X_O)^2 (1 + n_O^2/3) t_c \quad (3)$$

for the ^{17}O nucleus. The coupling constant is denoted by X_O (8.0 ± 0.2 MHz [20]) and n_O denotes the asymmetry parameter (0.75, gas value). The correlation time t_c is the zero frequency Fourier component of the correlation function of the interaction tensor, and contains all the dynamical features that can be obtained from NMR. Because the relaxation process is completely intramolecularly determined, this correlation time refers to the reorientational dynamics only. No differentiation has been made with respect to possible different classes

of water. If there exist several classes of water, the relaxation rates and derived properties may be interpreted as effective average quantities.

Now consider the results of the present study. Average values of the relaxation rates are compiled in Table 1. Figure 3 shows the ratio of the ^{17}O relaxation rates with respect to the pure water value ($R_f = 141 \text{ s}^{-1}$ [14]) versus the water weight fraction both in PEO (PEG 400) solutions in water and in the hydrophilic domains of the Brij 96 (9.3)-water creams, calculated according to eqn. (1). As shown in Fig. 3, the

TABLE 1

Relaxation rates of ^{17}O in PEO(9)-water and Brij 96 (EO9.3)-water mixtures at 25°C

f_w	Cream structure	Rate (R, s^{-1})
EO(9)-water		
0.381	—	1130
0.584 ^a	—	494
0.627 ^a	—	428
0.688 ^a	—	344
0.735 ^a	—	287
0.841 ^a	—	211
0.966 ^a	—	155
Brij 96 (EO9.3)-water		
0.381	L	1140
0.411	L	1010
0.479	VI	819
0.523	H	672
0.576	H	546
0.651	H	405

^aData from Breen et al. [13].

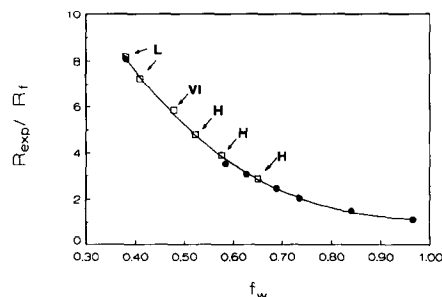


Fig. 3. Relative ^{17}O relaxation rates at 25°C in (●) PEO(9)-water mixtures and (□) hexagonal Brij 96 (EO8.5)-water creams. Pure water was used as a reference.

relaxation is completely governed by the water weight fraction. The relaxation does not depend on the structure of the system.

In the applied magnetic field range (2.1–9.3 T), the absence of any field dependence clearly indicates the longitudinal relaxation to be in the extreme narrowing limit. According to eqn. (3), in this situation the relaxation rate is directly proportional to the reorientational correlation time t_c . Although the quadrupolar coupling constant X_O may be sensitive to the intermolecular interactions, in PEO solutions this effect is rather small and in this context may be neglected (Van der Maarel, unpublished results). In consequence, the ratio R_{exp}/R_f directly reflects the ratio of the reorientational correlation times with respect to the pure water value: t_{exp}/t_f with $t_f = 1.95 \text{ ps}$ [20].

The water dynamics in PEO solutions have been discussed by Breen et al. [13]. For the purpose of this paper, it suffices to say that the present results clearly indicate that the cream structures do not influence the water reorientational dynamics within the hydrophilic domains; for a detailed discussion the reader is referred to Ref. [13]. Here the most important conclusions are summarized. The range of the polymer-solvent interaction is confined to one or two layers of water molecules around the PEO chain. In these layers the water reorientational correlation time (describing the rotational diffusion) is retarded by a factor of 2–8, depending on the number of water molecules dynamically perturbed by the macromolecular surface. As mentioned earlier, the experimentally determined relaxation rates may represent an average over several classes of water, which exchange at a fast rate; these may be bulk water on the one hand and water near the PEO chain on the other. However, in the lamellar cream having the lowest water content (water weight fraction of the cream 28%) and the PEO solution in which the water weight fraction is 0.38, there is just 1.5 water molecule per PEO unit available, so the presence of bulk or unperturbed water may be excluded. At this low water

concentration, the (mean) water reorientational mobility is retarded by a factor 8.

The results obtained by ^{17}O NMR and DTA are confirmed by literature data obtained by different techniques, of which self diffusion NMR has been mentioned already. Clunie et al. [25,26] measured the water vapour pressure and heat of mixing as functions of composition at 25°C for C_8EO_6 -water, C_{10}EO_6 -water and C_{12}EO_6 -water mixtures. The water activity and the heat of mixing are smooth functions with respect to the composition, with no measurable discontinuities at the boundaries between lamellar and hexagonal liquid crystalline phases, implying that there are no radical change in water-surfactant interactions. Volume and heat capacity measurements as a function of temperature across phase boundaries have confirmed that the lamellar phase/isotropic solution and hexagonal phase/isotropic solution transformations are phase transitions with very small volume and enthalpy changes. These latter observations were also confirmed by the differential scanning calorimetric study of Andersson and Olofsson [27].

CONCLUSIONS

Using ^{17}O NMR and DTA, no differences could be observed in the dynamical and freezing behaviour of water in a PEO-water solution and water in the hydrophilic domains of Brij 96-water creams. Using ^{17}O NMR, no influence of the various liquid crystalline phases (lamellar, viscous isotropic and hexagonal) on the dynamical behaviour of the water in the hydrophilic domains of the creams could be detected. These results are in accordance with literature data obtained by diffusion NMR and thermodynamical studies. The liquid crystalline structures of the creams, however, strongly influenced their rheological behaviour.

We conclude that the hydrophilic domains of the Brij 96-water creams may be regarded as PEO solutions in water. Since these hydro-

philic domains form a continuous phase, the tortuosity of which depends on the cream structure, these findings are important in the evaluation of the diffusional behaviour of drugs in these creams.

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