ELSEVIER

European Journal of Pharmaceutics and Biopharmaceutics 46 (1998) 51–59

European Journal of Pharmaceutics and Biopharmaceutics

Research paper

Interactions between fenoprofen sodium and poly (ethylene oxide)

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Received 21 July 1997; accepted 10 November 1997

Abstract

Interactions of the amphiphilic drug fenoprofen sodium (FNa) in solution below and above its critical micelle concentration with poly (ethylene oxide) (PEO) of different chain length (PEO 400 to PEO 20 000) and between a liquid crystalline formulation of fenoprofen (FLC; containing FNa, fenoprofen acid and water) and PEO were investigated, using surface tension measurements, viscometry, cloud point temperature measurements, [^{1}H]NMR, polarised light microscopy, transmission electron microscopy, and differential scanning calorimetry. Interaction between FNa solutions and PEO: the investigations suggest that an interaction starts below the critical micelle concentration (CMC) of FNa. This can be concluded from [^{1}H]NMR experiments (an upfield shift of the PEO proton signal was found at FNa concentrations below the CMC of FNa), surface tension measurements (absence of a critical association concentration) and cloud point temperature determinations. The surfactant does not seem to bind quantitatively on the PEO molecules (a higher FNa concentration was needed to cause the same upfield shift of the PEO proton signal than for more lipophilic surfactants, and no plateau phase in the surface tension reduction isotherm could be determined). Interactions were found to be independent from the chain length of the PEO. Interactions between FLC and PEO/pluronics: partial or complete dissolution of the fenoprofen mesophase (detected by [^{1}H]NMR, polarised light microscopy and transmission electron microscopy) occurred after addition of PEO at concentrations between 2 and 10% (w/w), independent from the molecular weight of the PEO. A comparable amount of water added to the liquid crystalline samples does not change the mesophase into a liquid crystalline dispersion or a micellar solution. The liquid crystalline particles in the dispersion formed by the addition of PEO, had a higher transition temperature into an isotropic phase (between 54°C and 57°C), than in liquid crystalline dispersions without polymer (40°C). The interactions between FNa and PEO can be interpreted in terms of a hydrophobic interaction with an association of the drug molecules on the polymer, i.e. the interaction between FNa and PEO occurs at a molecular rather than a micellar level. The interaction leads to a dissolution of the fenoprofen liquid crystal and the formation of an isotropic phase. No phase separation of the oily, amorphous, practically water insoluble fenoprofen acid could be found. Addition of PEO also seems to affect the composition of the remaining mesophase.

Keywords: Fenoprofen sodium; Poly (ethylene oxide); Polarised light microscopy; Transmission electron microscopy; Differential scanning calorimetry; Surfactant-polymer interactions

1. Introduction

In many pharmaceutical formulations, polymeric and amphiphilic substances are used together as active compounds or excipients. Interactions between these components can influence the physico-chemical properties of the dosage form and may alter the stability of the formulation and the liberation of the active component.

Not only pharmaceutical excipients such as emulsifiers, solubilising agents, and wetting agents [1] but also a great number of drugs have an amphiphilic molecular structure. These drugs are surface active and are able to form micelles in aqueous solutions at concentrations higher than their cri-

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0939-6411/98/$19.00
PII S0939-6411(97)00161-6

tical micelle concentration (CMC) and temperatures higher than their Krafft temperature. Examples of surface active, micelle forming drugs can be found in the group of phenothiazines [2], tricyclic and tetracyclic antidepressants [3], antihistamines, local anaesthetics, anticholinergics [4] and non-steroidal antiinflammatory drugs [5–7].

At higher concentrations some drugs also form aqueous liquid crystalline dispersions or single-phase lyotropic mesomorphous structures. Examples are salvarsan (type of liquid crystal: nematic) [8], disodium-chromoglycolate (nematic, hexagonal) [9], nafoxidin-HCl (hexagonal, cubic, lamellar) [10], diethylammonium flufenaminic acid (lamellar) [11], polidocanol (lamellar, hexagonal) [5], fenoprofen sodium (lamellar) [5], ketoprofen sodium (lamellar) [5] and diclofenac salts (lamellar) [6].

In the present study the non-steroidal antiinflammatory drug fenoprofen sodium (FNa) is used as amphiphilic substance. The structural formula (Fig. 1) reveals that FNa consists of an anionic polar head group and a predominantly aromatic lipophilic tail group (diphenyl ether structure). In previous studies it could be shown that FNa, besides its ability to form a thermotropic mesophase (type smectic A) [12], is a surface active, micelle forming drug, which is able to form an aqueous lamellar mesophase or a dispersion of a lamellar mesophase in a continuous aqueous phase at concentrations higher than 55% (w/w) of FNa and temperatures higher than 38°C or at room temperature after the addition of the oily, amorphous fenoprofen acid [13]. FNa therefore is a suitable amphiphile to investigate interactions of a polymeric substance with a surfactant in its aqueous micellar and liquid crystalline form.

The aim of the study was to investigate interactions of the drug in solution and liquid crystalline form with a non-ionic polymeric substance (in a previous study interactions of FNa with an ionic polymer (gelatin) were investigated [14]).

Poly (ethylene oxide) (PEO) was chosen, because it is available in different molecular weights and is freely soluble in water.

For the investigation of polymer-surfactant interactions in aqueous solutions several methods such as viscometry, NMR, surface tension measurements, precipitation and solubilisation experiments are described and were used in this study. For reviews see [15–17]. For the investigation of polymers with surfactants in the liquid crystalline state, microscopical and thermo-analytical techniques were used.

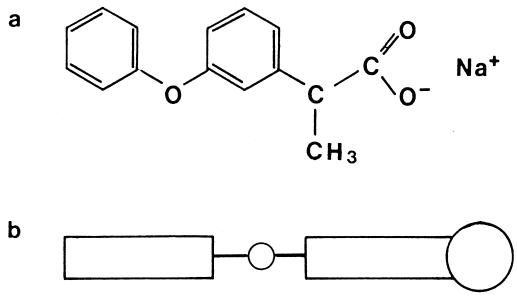

Fig. 1. (a) Structural formula of FNa, (b) schematic representation of polar and non-polar areas of FNa.

2. Materials and methods

2.1. Materials

2.1.1. Fenoprofen

FNa and fenoprofen acid were prepared from fenoprofen calcium (Eli Lilly, Gießen, Germany). The calcium salt was dispersed in an aqueous HCl-solution (10% w/v). To extract the free acid, the dispersion was shaken several times with dichloromethane. After evaporation of the dicloromethane, fenoprofen acid was obtained as a clear, yellow liquid of which the refractive index at 20°C was 1.569. According to the Merck Index the refractive index is 1.574 [18]. To prepare the sodium salt, the acid was dissolved in an equimolar amount of 1 N NaOH. The solvent was evaporated until FNa crystallised as dihydrate with a water content of 12%, determined by thermogravimetry (TGA 2/TADS 3600, Perkin Elmer, Überlingen, Germany) and by KARL-FISCHER titration (701 KF Titrino/703 Ti, Metrohm, Herisau, Switzerland). The melting point of the sodium salt in a closed system, determined by differential scanning calorimetry (DSC) was 79°C (DSC2-C/TADS 3600, Perkin Elmer, Überlingen, Germany).

2.1.2. Poly (ethylene oxide)

The PEO had nominal average molecular weights of 300, 400, 1500, 6000, 12 000, and 20 000 according to the designation of the PEO by the manufacturer (Hüls AG, Marl, Germany).

The average molecular weight of the short-chain PEO was experimentally confirmed by determination of the hydroxyl number (Method V.3.4.3. A of the German Pharmacopoeia 10 (DAB10) [19]) and by viscosity measurements of aqueous PEO solutions of different concentrations, using a modified Mark–Houwink equation [20]. The molecular weight distribution of the longer-chain PEO was determined using MALD-TOF-MS, as a non-fragmenting mass-spectroscopic method (Reflex MALD-TOF-MS, Bruker GmbH, Rheinstetten, Germany. Matrix material: 2,5-dihydroxybenzoic acid). The molecular weights of the polymers were normal distributed and the average molecular weight was found to be higher than the nominal molecular weight according to the designation of the producer (PEO 6000: average molecular weight as determined with MALD-TOF: 7000, PEO 20 000: 22 000 and PEO 12 000: 16 000). To avoid confusion, the different PEO in this study are named, according to the manufacturer's designation.

2.1.3. Poly (ethylene oxide)-poly (propylene oxide)-copolymer

Pluronic F108 (BASF Parsippany, NJ, USA; molecular weight according to the manufacturer, 14 600) was used in

this study, as a polymer containing less hydrophilic (polypropylene oxide) groups.

2.1.4. Water and sodium chloride

Water was used in double distilled quality. Sodium chloride (NaCl) was of analytical grade (Natriumchlorid z. A., Merck, Darmstadt, Germany)

2.2. Methods

2.2.1. Surface tension measurements

Surface tension measurements were carried out using a processor tensiometer (Tensiometer K12, Krüss, Hamburg, Germany) equipped with a Wilhelmy-plate. The solutions were stirred for 1 min and then allowed to equilibrate for 2 min before each measurement. Samples were prepared in triplicate. Every point of measurement was automatically determined 10 times. The relative standard deviations (SDs) of the 10 measurements for each sample were smaller than 0.05%. The SD of the measurements for each surfactant concentration was smaller than ±1 mN/m. The measurement temperature was adjusted at 20 ± 0.2°C by using a water thermostat.

2.2.2. Viscosity measurements

Viscosity measurements were performed using Ubbelohde capillary viscometers Type 52510/l (k = 0.009634) and 52503/Oc (k = 0.002759) (Schott-Geräte, Hofheim, Germany). Samples were checked for Newtonian flow, using a rotational viscometer with a cup and bob system (RV100/CV100, Measuring system ME15 and ME30, Haake, Karlsruhe, Germany). The measurement temperature was adjusted at 20 ± 0.1°C by using a water thermostat.

2.2.3. Cloud point measurements

Twenty millilitres of the aqueous polymer solution (10% or 20% (w/v)) containing 0–8% (w/v) of NaCl and/or 0–14% (w/v) of FNa, were heated in a glass vial at a heating rate of 5 K/min. The solution was stirred with a magnetic stirrer. The temperature was measured using a thermometer which also closed the vial. The temperature at which clouding was observed during heating was determined (t_1). The sample was subsequently allowed to cool (cooling rate was not controlled) and the temperature at which clouding disappeared was recorded (t_2). The mean of t_1 and t_2 gave the cloud point temperature. Each measurement was performed in triplicate. SDs of the cloud point determinations were smaller than ±1°C.

2.2.4. [^{1}H]NMR experiments

[^{1}H]NMR experiments of polymer-drug mixtures in deuterium oxide (D_2O, Deuterium Oxide for NMR; Merck, Darmstadt, Germany) at a temperature of 20°C were carried out with a Bruker AM 400 MHz (Bruker analytische Messtechnik GmbH, Rheinstetten, Germany). Samples were prepared in triplicate. SDs in the chemical shift determinations (δ = 0.1–8.9 ppm) were smaller than ±0.002 ppm.

2.2.5. Polarised light microscopy (PLM)

Samples were investigated using a Photomicroscope III (Zeiss, Oberkochen, Germany) equipped with crossed polarisers and a λ-sheet. For hot stage investigations (HSPLM) a heating and cooling device (FP 52 and FP 5, Mettler AG, Gießen, Germany) was inserted into the optical bench. Heating rate was 5 K/min.

2.2.6. Transmission electron microscopy (TEM)

Samples were cryo-fixed with a jet-freeze device JFD 030 with liquid propane (Baltec, Walluf, Germany) The frozen samples were freeze fractured at −100°C at a pressure of 5×10^{-6} bar (BAF 400, Balzers, Wiesbaden, Germany). Shadowing of the samples was performed with platinum/carbon (layer thickness 2 nm) at 45° and with carbon (layer thickness 20 nm) at 90°. The replica were cleaned with chloroform/methanol (1:1 (v/v)) and water. Replica on uncoated grits were viewed with a transmission electron microscope at 80 kV (EM-300, Philips, Kassel, Germany) at various magnifications.

2.2.7. Differential scanning calorimetry (DSC)

Measurements were performed on a DSC 2-C (Standardcell 319–0006) with Thermal Analysis Data Station TADS 3600 (Perkin Elmer, Überlingen, Germany). Samples in hermetically sealed pans were heated at a scan rate of 5 K/min with an empty pan serving as reference.

3. Results

3.1. Interactions between FNa and PEO in FNa solutions

3.1.1. Surface tension measurements

Surface tension measurements have first been used by Jones [21] to study interactions between surfactants and non-ionic polymers. A concept of transition points was developed, which is illustrated in Fig. 2. T1 indicates the critical association concentration (CAC) of the surfactant to the polymer, T2′ represents the saturation concentration of bound surfactant molecules on the polymer and at T2 regular micelles are formed.

In Fig. 3 the surface tension reduction isotherm (at 20°C) of FNa in aqueous solution with and without the addition of 0.025% (w/v) PEO 6000 is shown. In both cases the addition of FNa to an aqueous solution led to a decrease in the surface tension. A critical concentration of 1.5×10^{-2} mol/l FNa was found, but due to the unusual micellisation behaviour of FNa, this concentration cannot be regarded as the CMC of FNa, which was determined using bulk methods to be 1.2×10^{-1} mol/l FNa [14,22].

The slope of the isotherm was less steep in the case of a polymer containing solution. The lower starting value for

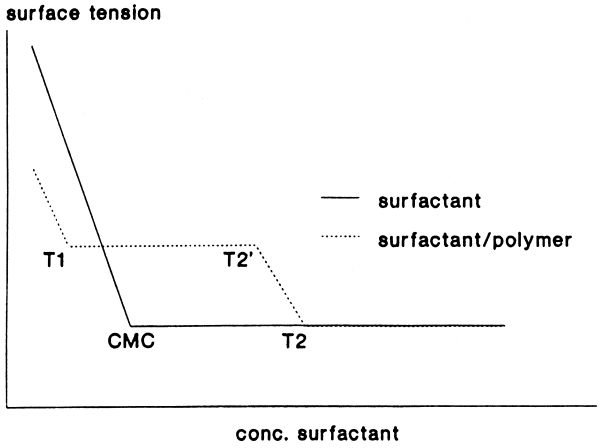

Fig. 2. Schematic surface tension versus concentration plots of a surfactant in the presence of a complexing polymer (dashed line) and without. T1 indicates the critical concentration of binding, T2′ is the saturation concentration and at T2 regular micelles are formed.

the surface tension of the polymer solution was due to the surface tension reduction caused by the added polymer. The reduction of the surface tension in the polymer containing solution resulted in a steeper slope of the isotherm at FNa concentration higher than 2×10^{-2} mol/l. At 6.5×10^{-2} mol/l FNa the surface tension reached a constant value of 38 mN/m.

The results of the surface tension measurements suggest that an interaction between the polymer and the surfactant takes place in the aqueous solution. There are however, some differences to the Jones concept described above. A CAC (T1-concentration) could not clearly be detected. Although the presence of a polymer reduces the decrease of surface tension on addition of FNa, a plateau phase, in which addition of surfactant does not lead to any surface tension reduction could not be found. On the other hand, the T2′- and the T2-concentration could be detected (2×10^{-2} and 6.5×10^{-2} mol/l FNa, respectively).

The absence of a clearly detectable T1-concentration can be explained by an association process between the drug and the polymer, which takes place already at low FNa concentrations. The shape of the isotherm can be caused by a non-quantitative binding of FNa molecules to the polymer. In this case the free surfactant could reduce the surface tension of the solution. It is also possible that a surface active surfactant-polymer-complex is formed, which leads to a decrease of the surface tension on addition of the drug. In fact, surface tension reduction isotherms of surfactants in presence of a polymer not necessarily exhibit a plateau phase, although interactions between both components have clearly been demonstrated by other methods [23]. As a result of either process a quantification of the amount of FNa bound per monomer unit of PEO from the surface tension reduction isotherm was not possible.

While increasing the amount of PEO the T2 value shifted to higher FNa concentrations (as could be expected, because more ‘binding sites’ for the surfactant are available) using the same amounts of PEO of different chain length did lead to almost identical surface tension reduction isotherms, indicating that the interactions between FNa and PEOs are not depending on the chain length of the PEO.

3.1.2. Viscosity measurements

Tensiometry is an analytical method, which detects changes in the surface of a solution. Viscometry on the other hand is a bulk method to investigate the interactions between polymers and surfactant. The kinematic viscosities of 0.025% (w/v) PEO solutions were determined as a function of added FNa. Fig. 4 shows that the viscosities of the aqueous polymer solutions depended on the molecular weight of the PEO used, and that they increased with increasing chain length. The increase in the viscosities of the polymer solutions upon adding FNa however, was not different to the viscosity increase of aqueous, polymer-free solutions of FNa. Using PEO and sodium lauryl sulphate (SLS), a strong increase in the viscosities of the polymer solutions could be detected by Francois et al. at the T1-concentration [24]. It was assumed that the reason for this increase in viscosity was the introduction of a negative charge on the polymer, due to the association of the surfactant with the polymer. This leads to stronger repulsion forces, changing the conformation of the polymer and consequently resulting in an increase in the viscosity. The

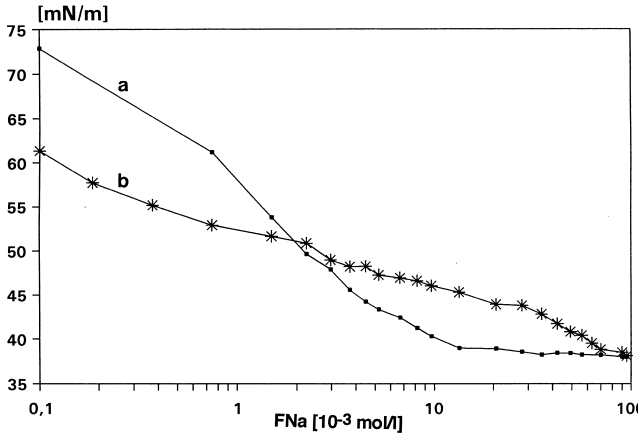

Fig. 3. Surface tension reduction isotherm of FNa in aqueous solution (a) without polymer and (b) in presence of 0.025% PEO 6000.

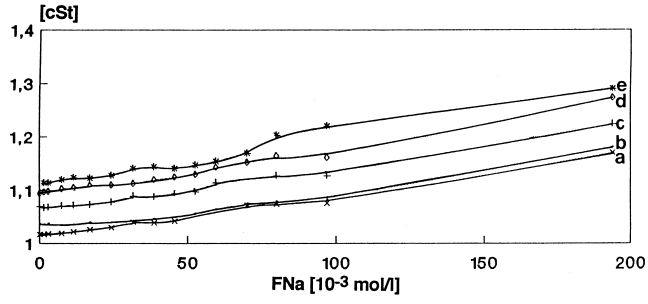

Fig. 4. Kinematic viscosities of aqueous solutions of FNa (a) without polymer, (b–e) in presence of 0.025% PEO ((b) PEO 400; (c) PEO 6000; (d) PEO 12 000; (e) PEO 20 000).

results were obtained using very long chain PEO, with molecular weights up to 2×10^6, and it can be assumed that the viscosity increasing effect of reducing the coil formation of the PEO should be the more prominent the higher the molecular weight of the polymer is. In this study, only comparatively short chain PEO molecules were used, which may have been too small, to allow detection of discontinuities or critical concentrations in the viscosity versus surfactant concentration plot.

3.1.3. Cloud point measurements

The determination of the cloud point temperature is a bulk method that detects effects of a polymer surfactant interaction on the behaviour of the polymer in a solution, rather than that of the surfactant. With increasing temperature, the solubility of PEO in aqueous solutions decreases and at a certain concentration, depending on the chain length of the polymer, phase separation occurs, transforming the solution into a polymer-rich phase and a polymer-poor aqueous phase. The temperature at which this phase separation occurs is referred to as the cloud point. As reasons for the precipitation of a PEO-rich phase, increasing attractive interactions between single polymer molecules and a breakdown of the ordered water structure around the polymer are discussed [25].

An interaction between PEO and an ionic surfactant can result in an increase of the cloud point temperature, because the bound surfactant introduces a charge to the polymer, therefore making the complex more polar [26]. To allow the determination of the cloud point temperature in the experimental set-up chosen, it was necessary to add NaCl to the PEO 20 000 solution. Fig. 5a shows that addition of NaCl led to a linear decrease of the cloud point temperature. If FNa was added to a solution containing PEO 20 000 and 2% NaCl, FNa initially caused the cloud point temperature to decrease but higher FNa concentrations raised the cloud point temperature. To determine the effect of FNa alone on the cloud point, Pluronic F108 was used as polymer, because its cloud point temperature was below 100°C in the experimental set-up chosen (Fig. 5b). While NaCl caused a decrease, FNa led to an increase of the cloud point temperature. Also in the case of pluronic, in presence of NaCl, the addition of FNa caused a minimum in the cloud point versus FNa concentration curve.

An increase of the cloud point temperature on addition of FNa can be regarded as an indication of an interaction between the surfactant and the polymer, i.e. a binding of the surfactant on the polymer and therefore an increase of the polarity of the complex compared to the polymer alone. It is however necessary to consider that the FNa can be expected to interact with water to disrupt the water structure, this in turn could alter the interaction of water with the surfactant and the polymer. Hence the interaction may be equally an indirect one mediated through water. The direct increase of the cloud point already at low surfactant concentrations in the case of the pluronic solution points at

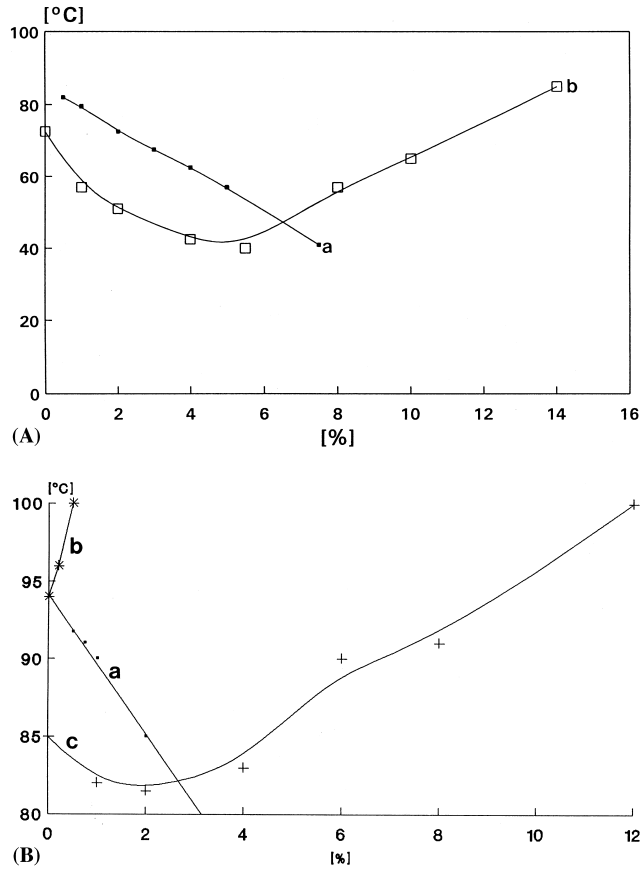

Fig. 5. (A) Cloud point temperature of PEO 20 000 versus the concentration of (a) NaCl and (b) FNa (in presence of 2% NaCl). (B) Cloud point temperature of pluronic F108 versus the concentration of (a) NaCl and (b) FNa and (c) FNa (in presence of 2% NaCl).

direct interaction between both substances at FNa concentrations below the CMC. Only in the case of the presence of NaCl in the polymer solution, added FNa caused an initial decrease of the cloud point temperature. NaCl increases the polarity of the solvent. Carlsson et al. [26] found that the addition of small amounts of a short chain cationic surfactant with a high CMC can also directly (i.e. without NaCl being present in the solution) lead to an initial decrease of the cloud point temperature, due to a salt effect of the surfactant. The authors concluded that only above the CMC the surfactant molecules (i.e. micelles) interact with the polymer, increasing the cloud point temperature. This however, is not the case in the system FNa/pluronic.

If NaCl is present in the solution, the influence of FNa on the cloud point temperature is comparable to that of SLS on the cloud point of ethyl-hydroxyethyl cellulose [26]. According to Carlsson et al., the initial decrease of the cloud point temperature on addition of a surfactant in the presence of NaCl is caused by the fact that binding of the surfactant has two effects on the polymer. On the one hand binding of surfactant increases the polarity of the complex, which should lead to an increase in the cloud point temperature. On the other hand the surfactant may change the con-

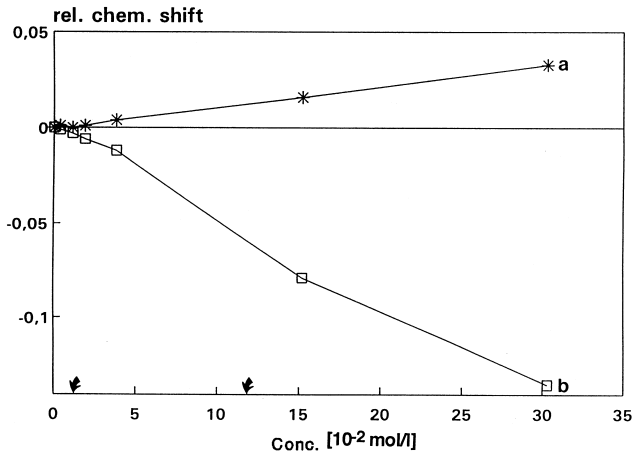

Fig. 6. Relative chemical shift of the proton signal of PEO 12 000 versus the concentration of added (a) FNa and (b) NaCl. The intercept with the ordinate represents the chemical shift of the PEO proton signal at 3.74 ppm. The arrows indicate the two critical concentrations of aqueous FNa solutions detected using either surface or bulk methods [22].

formation of the polymer, thus leading to a decrease of the cloud point temperature. The latter effect becomes more important in the presence of electrolytes as the polarity increasing effect of the surfactant on the polymer is repressed, due to the presence of the salt and only becomes important at higher surfactant concentrations.

3.1.4. [^{1}H]NMR investigations

Addition of FNa to a PEO solution in D_2O led to an upfield shift (to smaller ppm values) of the proton signal of PEO. Fig. 6 shows that the signal shifts nearly linearly when adding increasing amounts of the drug. A minimal critical surfactant concentration, necessary to cause an upfield shift could not be detected.

Addition of NaCl to a PEO solution has an opposite effect on the PEO proton signal shift.

The effect of FNa on the polymer was the same, independent from the chain length of the PEO.

Gao et al. [27] could show that sodium-ω-phenyldecanoate (SPD) also causes an upfield shift of the proton signal of PEO. This effect was observed at surfactant concentration which were 5–10 times lower than the FNa concentrations in this study. SPD however, is more lipophilic than FNa, indicated by the fact that the CMC of SPD is about 10 times lower than the CMC of FNa determined with bulk methods [22].

3.2. Interactions between a FNa mesophase and PEO

To investigate the influence of PEO on liquid crystalline formulations of FNa, a lamellar mesophase of fenoprofen (FNa, 40% (w/w); fenoprofen acid, 25% (w/w); and water, 35% (w/w)) was formulated. Up to 10% (w/w) of PEO of different chain length (mainly PEO 400 and PEO 12 000) were added.

3.2.1. Macroscopical observations

The gel-like mesophase transformed into a viscous, transparent liquid at PEO concentrations higher than 3% (w/w). The viscosity of the liquid decreased with increasing PEO concentration. The behaviour of the system was independent from the chain length of the PEO.

3.2.2. PLM investigations

In the PLM the lamellar phase exhibited typical textures (oily streaks, maltese crosses and pseudoisotropic texture). After addition of 1% (w/w) PEO the textural appearance changed and the number of maltese crosses strongly increased. After addition of 3% (w/w) PEO an isotropic second phase developed, which could be regarded as the dispersed phase up to a PEO concentration of 4.5% (w/w). At higher PEO concentrations isolated liquid crystalline areas could be observed and at 7% (w/w) PEO the system was completely isotropic. The behaviour of the mesophase upon addition of PEO was independent from the chain length of the PEO added.

The liquid crystalline areas only show a weak anisotropy in the PLM (Fig. 7). The reason for this observation, as well as for the macroscopical transparency of the biphasic systems, despite the fact that they contain a dispersed mesophase (in contrast to the turbid aqueous polymer-free liquid crystalline dispersions of fenoprofen), is that the refractive indices of the mesophase and the polymer containing isotropic phase both are around $n_D^{20} = 1.49$.

3.2.3. TEM investigations

The liquid crystalline phase of the biphasic PEO containing formulations showed a great number of concentric structural defects (tori, DUPIN-cyclides). This could be expected from the textural appearance of the mesophase (Fig. 8a). The lamellar layers did not show any ‘popping off’, a phenomenon which was often found in the freeze fractures of aqueous, polymer-free dispersions of the lamellar phase of fenoprofen. These structures were artefacts, caused by the formation of crystalline ice in the water layer of mesophases that contain high amounts of water [28].

The isotropic PEO-containing formulations did not show any liquid crystalline structures. Their appearance corresponds to that of a solution (Fig. 8b).

3.2.4. [^{1}H]NMR investigations

The proton signals of molecules in the liquid crystalline state are usually very broad, due to the restricted mobility of the molecules in the system. Fig. 9a shows the [^{1}H]NMR spectrum of the single-phase, liquid crystalline fenoprofen formulation. Dilution of the mesophase with water (fenoprofen acid) ultimately leads to a micellar solution (reversed micellar solution), exhibiting much less broad signals (Fig. 9b,c). Compared to the spectra of micellar and reversed micellar PEO-free solutions, the PEO-containing solutions showed an intermediate behaviour with respect to signal broadening and signal shift. This can be explained by the

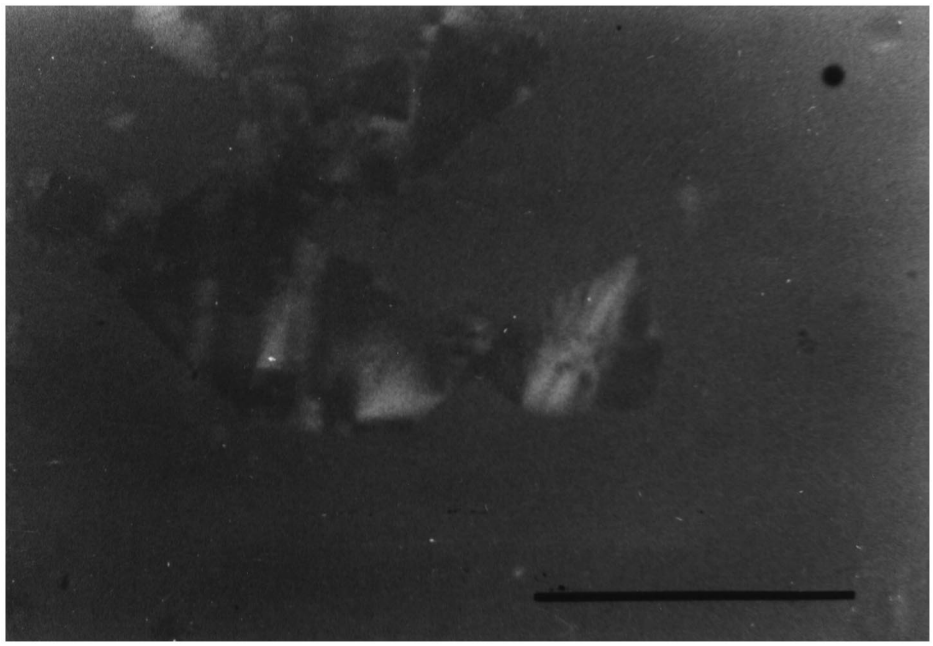

Fig. 7. PLM micrograph of the fenoprofen mesophase after addition of 6% (w/w) PEO 12 000. Bar represents 100 μm.

intermediate viscosity and content of fenoprofen of the PEO-containing formulation, compared to the polymer-free aqueous and oily solutions. As could be expected from the NMR investigations in diluted systems, the proton signal of PEO is strongly shifted to the higher field (3.10 ppm).

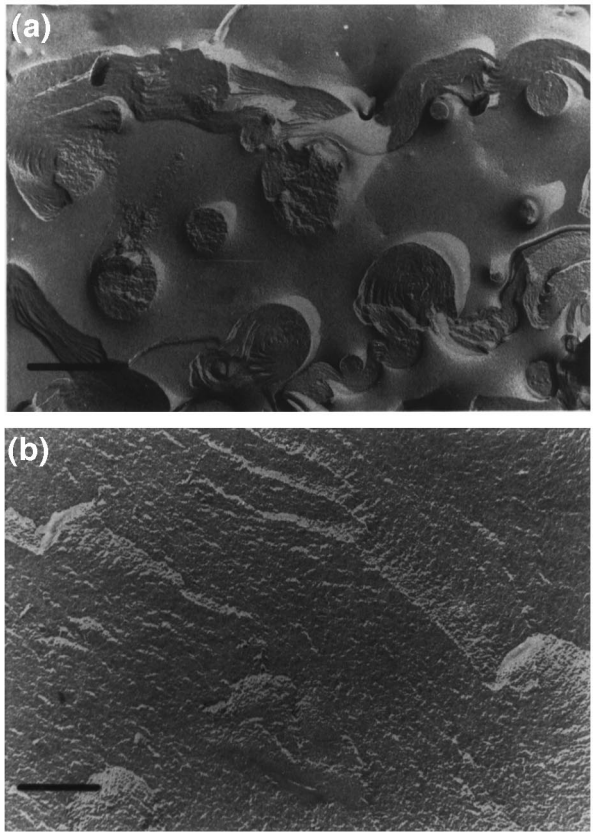

Fig. 8. (a) TEM micrograph of the fenoprofen mesophase after addition of 5% (w/w) PEO 12 000 (b) TEM micrograph of the fenoprofen mesophase after addition of 7% (w/w) POE 400. Bar represents 200 nm.

3.2.5. DSC and HSPLM investigations

The phase transition temperature of single phase lamellar mesophases of fenoprofen decreased with increasing amounts of water incorporated in the lamellar mesophase from 64°C to 43°C. Aqueous dispersions of fenoprofen liquid crystals transformed into an isotropic phase at tem-

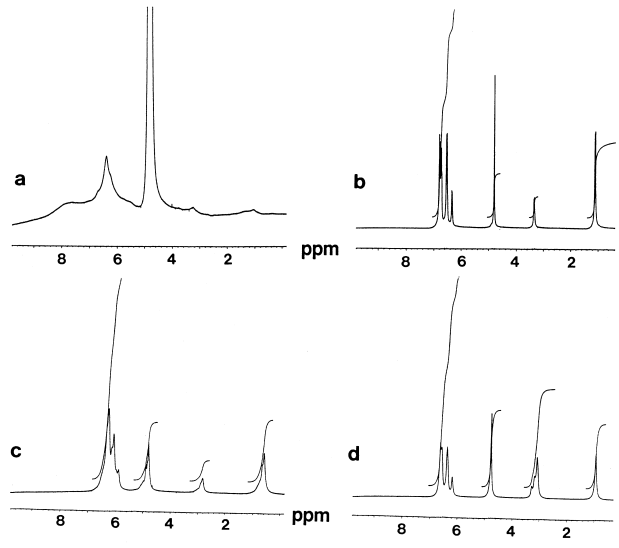

Fig. 9. [^{1}H]NMR spectra of different fenoprofen formulations: (a) fenoprofen liquid crystal, (b) micellar solution prepared from (a) by adding water, (c) reversed micellar solution, prepared from (a) by addition of fenoprofen acid, (d) isotropic phase prepared from (a) by addition of PEO 12 000.

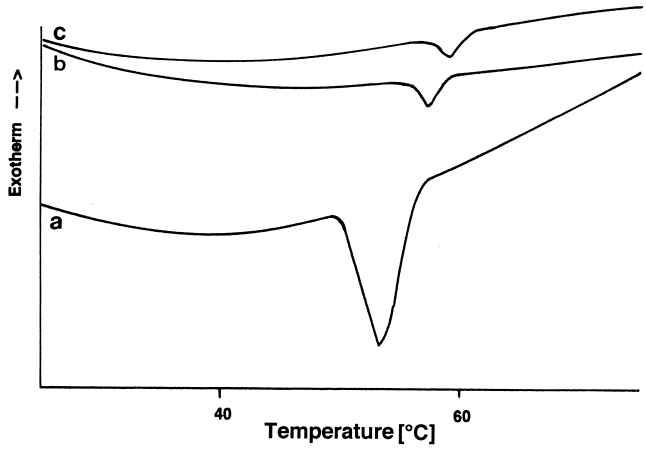

Fig. 10. DSC curves of different fenoprofen formulations: (a) fenoprofen liquid crystal, (b) liquid crystalline dispersion prepared from fenoprofen liquid crystal by addition of 3.2% (w/w) PEO 12 000, (c) liquid crystalline dispersion prepared from fenoprofen liquid crystal by addition of 4.1% (w/w) PEO 12 000.

peratures around 40°C [13,28]. The liquid crystalline dispersions which formed upon addition of PEO on the other hand exhibited higher phase transition temperatures than the original mesophase (55–57°C) (Fig. 10), which correspond to the transition temperature of a single phase fenoprofen liquid crystal containing 33–34% of water. The transition enthalpies of the dispersed systems however, were lower, due to the smaller amount of mesophase in the dispersion, compared to the single phase liquid crystal.

4. Discussion

The results of this study suggest that the association of FNa and PEO starts below the CMC of FNa, i.e. the interaction between FNa and PEO occurs on a molecular rather than a micellar level. This can be concluded from the upfield shift of the PEO proton signal at FNa concentrations below the CMC of FNa, the absence of a T1 concentration in the surface tension experiments and the increase of the cloud point temperature of the pluronic (assuming a similar type of interaction between FNa and pluronic and FNa and PEO). Thus a stepwise association of the drug molecules on the polymer can be suggested. The surfactant however, does not seem to bind quantitatively on the PEO molecules. This can be concluded from the fact that higher FNa concentrations than SPD concentrations are needed to cause the same upfield shift of the PEO proton signal, and that no plateau phase in the surface tension reduction isotherm could be determined.

Two models are discussed in the literature for interactions between anionic surfactants and PEO, both based on a hydrophobic interaction between parts of the lipophilic tail group of the surfactant and the ethylene groups of PEO. In the first model (based on experiments using PEO and SLS) spherical surfactant micelles are surrounded by the PEO molecules, so that an interaction mainly occurs between the ethylene groups of the surfactant in vicinity to the ionic head group and the ethylene groups of the PEO [23]. In the other model (based on experiments using PEO and SPD) most of the PEO monomer units are located in the interior of the aggregate, in the same region of the micelle than the terminal phenyl group of the surfactant [27]. While the first model implies a minimal molecular weight of the PEO molecule, necessary to cause an interaction, this is not the case in the second model. In opposite to the system SLS-PEO [29] a minimal chain length, required for an FNa-PEO interaction could not be detected, thus pointing at the second interaction model to be more likely for the FNa-PEO interaction. It is interesting to notice that both SPD and FNa, in opposite to SDS, have an aromatic structure in their lipophilic tail groups.

The investigation of the interactions between the FNa mesophase and PEO showed that already low concentrations of the polymer led to changes in the structure of the system, which cannot be explained by a simple dilution effect. After addition of 10% (w/w) of water to the model liquid crystal the formulation is still a single phase mesomorphous system and further addition of water will lead to an aqueous liquid crystalline dispersion (see ternary phase diagram in [13]).

The isotropic PEO containing solution is able to solubilise the practically water insoluble fenoprofen acid. No phase separation of an oily fenoprofen acid phase could be observed, after addition of PEO.

The results of the DSC and the HSPLM investigations as well as the absence of any ‘popping off’ artefacts in the TEM studies suggest that PEO not only has a dissolving effect on the liquid crystalline phase of fenoprofen, but also changes the composition of the remaining mesophase, increasing its transition temperature, possibly due to binding of water from the mesophase.

Acknowledgements

We want to thank the Eli Lilly Company for supporting us with fenoprofen calcium. We also acknowledge the availability of the TEM at the Department of Botanics, Technical University of Braunschweig (TUBs), the availability of the MALD/TOF-MS at the GBF, Braunschweig, and the availability of the NMR at the Department of Organic Chemistry at the TUBs.

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