Colloid & Polymer Science Colloid Polym Sci 272:228–235 (1994)

Lidocaine and soyasterole-PEG-16-ether – investigations on the interaction between an amphiphilic drug and a nonionic surfactant in aqueous solution

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Abstract: In order to study the interactions between the surface active local anaesthetic drug lidocaine and the nonionic surfactant soyasterole-PEG-16-ether firstly the self association of the drug in aqueous solution was investigated by different methods. Transmission electron microscopy hinted at micellization and surface tension measurements resulted in a CMC of 12.9% (salt form) and 0.08% (base form), respectively, whereas solubilization experiments, NMR spectroscopy and osmotic pressure measurements obviously disproved the existence of drug micelles. The detected CMC only meant a surface saturation and the TEM pictures probably showed artifacts. In diluted systems containing both drug and surfactant no formation of mixed micelles took place, as pointed out by the tensiometric determination of the CMC of the mixtures showing no minimum in the CMC/%drug-curve. Also, gel permeation chromatography clearly separated surfactant micelles and drug molecules. In contrast to this, evident interactions between the base form of the drug and the surfactant occurred when the drug concentration was increased: the dynamic viscosity of the systems rose distinctly, probably caused by growth of the surfactant associates to a more rodlike form. The salt form had nearly no influence on the viscosity of the preparations.

Key words: Nonionic surfactants – lidocaine – micelles – interactions – surface tension – viscosimetry – gel permeation chromatography (GPC)

Introduction

It is well known that amphiphilic drugs are able to participate in the microstructure of colloidal surfactant associates such as micelles, vesicles or liquid crystalline phases: depending on their hydrophilic/lipophilic properties they can be localized in different regions of the particles, thus influencing size and shape of the aggregates formed. The cubic mesophase of a surfactant, for example, is transformed into a reverse hexagonal structure on addition of the base form of a local anaesthetic, while admixture of the salt form induces the formation of a lamellar liquid crystal [1, 2]. In contrast to this, the same local anaesthetic in its base form changes a higher-concentrated micellar solution of a different surfactant into a semi-solid, gel-like preparation of hexagonal structure, while the salt exhibits hardly any influence [3, 4]. In diluted surfactant solutions often mixed-micelle formation with amphiphilic, partly self-associating drugs can be noticed. Typical examples are antihistamines [5, 6], tri- and tetracyclic psychiatrics [7], local anaesthetics [8, 9], antibiotics [10, 11] and preservatives of different chemical structures [12, 13]. Practical importance have all these phenomena for changes in drug delivery from such systems and a – partly considerable – loss in drug efficacy.

Mostly drug containing surfactant preparations are either investigated and characterized for rather low concentrations of both components (close to the CMC of the surfactant) or higher concentrations at which already liquid crystalline states occur. The starting point of the present investigations was the above mentioned

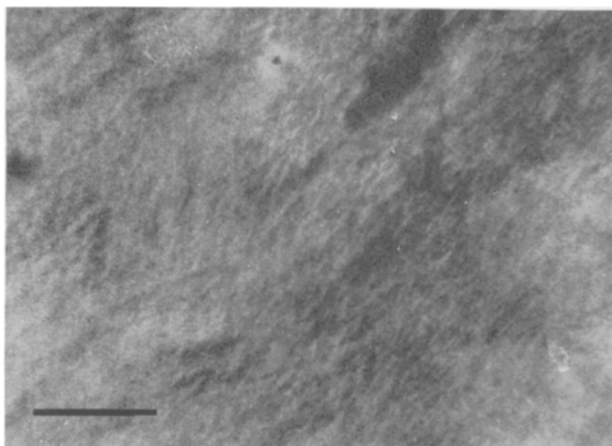

Fig. 1. Polarized light micrograph of a 40% solution of E 16 after admixture of 2% lidocaine base, bar 50 μm

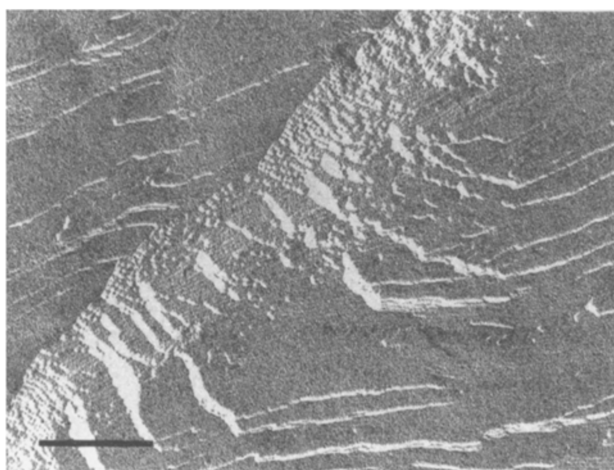

Fig. 2. Transmission electron micrograph of a freeze-fractured and replicated 40% solution of E 16 after admixture of 2% lidocaine base, bar 250 nm

observation that a 40% solution of soyasterole-PEG-16-ether (E 16), a highly viscous liquid being isotropic in polarized light microscopy, is transformed into a system of hexagonal liquid crystalline structure on addition of 2% lidocaine base. This is clearly shown in Figs. 1 and 2. The paper therefore tries to establish a connection between the phase transformation of a micellar solution of the nonionic surfactant E 16 by the local anaesthetic lidocaine and the potential interaction of both substances in the particle interface in diluted systems.

Materials and methods

The local anaesthetic drugs used were lidocaine HCl monohydrate and lidocaine base (Astra, Södertälje, Sweden).

The applied nonionic surfactant was soyasterole-PEG-16-ether (Generol 122 E 16, Henkel, Düsseldorf, FRG) abbreviated in the further text as E 16.

The mixture of a 40% solution of E 16 and 2% lidocaine base was prepared by stirring the solution of the surfactant with the powdered drug for 12 h.

The surface tension measurements were carried out at a temperature of 293 K with an automatic tensiometer (Dr. R. Wobser KG, Lauda-Königshofen, FRG). For the measurements of the pure drug solutions a Lecomte de Nouy ring was used and the samples were prepared directly in the measuring vessel with bidistilled water. For the determination of the CMC of the drug/surfactant mixtures a Wilhelmy plate was used and the samples were prepared by diluting different amounts of a stock solution in the measuring vessel. After an equilibration time of 14 h the measurements were carried out.

The polarized light micrographs were taken with a photomicroscope laborlux pol (Leitz, Wetzlar, FRG).

For the freeze-fracture-technique the samples were fixed in melting nitrogen at about 63 K. The frozen samples were then freeze fractured at a temperature of 173 K and shadowed with platinum/carbon at an angle of 45° (BAF 400, Balzers, Wiesbaden, FRG). After cleaning, the obtained replica were observed by a transmission electron microscope (EM 109, Zeiss, Oberkochen, FRG) with an accelerating voltage of 80 kV.

The solubilization experiments were performed by stirring the drug solutions with an excess amount of powdered sudanred B (Merck, Darmstadt, FRG) for 72 h, separating the unsoluble dye by giving the mixture through a 0.22 μm-filter and measuring the light absorption at λ_{max}, which was determined by taking a spectrum between 400 nm and 800 nm (photometer UV-160, Shimadzu, Duisburg, FRG). These λ_{max} were found between 502 nm and 526 nm.

Osmotic pressure measurements of the drug solutions were carried out with a vapor pressure osmometer (Knauer, Bad Homburg, FRG).

Nuclear magnetic resonance spectroscopy was performed with a JNM GX-400 FT-NMR-spectrometer (Jeol, Eching, FRG). The solvent used was D_2O (Merck, Darmstadt, FRG).

For the gel permeation chromatography (GPC) investigations a chromatography glass tube (inner diameter: 1 cm) closeable by a tap was filled with Fractogel TSK HW 40 (Merck, Darmstadt, FRG), so that the height of the gel bed was 15 cm. The sample volume given onto the gel was 5 ml. It was eluted with bidistilled water under a pressure of 150 cm water column upon it, so that the flow rate was 0.5 ml/min. The eluted liquid was collected in intervals of 10 min and the UV-absorption measured at $\lambda = 270$ nm and $\lambda = 293$ nm (photometer UV-160, Shimadzu, Duisburg, FRG).

Results and discussion

Colloidal-chemical characterization of the drug

In literature lidocaine HCl is described as one of a few surface active local anaesthetics showing no self-association in aqueous solution [8]. The method used here, the measurement of the surface tension of aqueous solutions with increasing concentration, showed no discontinuity (i.e., no CMC) in the curve when performed up to a concentration of 5% (w/w). It was not possible to detect discrete particles of a certain micellar weight by measurements of the refractive index increment and the turbidity of the solutions. But, if the concentration range is extended until nearly saturation is reached ($\sim$58%), as shown in Fig. 3, there clearly occurs a kink at a concentration of 12.9% pointing at micelle formation (the value was obtained by regression of the two linear parts of the curve and determining the point of intersection). Even for the base form a similar result is obtained with a characteristic concentration of 0.08%, but as the solubility of lidocaine base in water is only 0.38% at 25 °C [14], this system was not further investigated. Nevertheless, the existence of micelles cannot be deduced from this results alone, as only a conclusion from processes in the interface to the events in the bulk is made, but no direct proof for their presence is furnished.

A further hint is given by the direct visualization of the microstructure in a TEM-picture of a freeze fractured solution having a concentration beyond the CMC showing a large number of globular aggregates with a size of 12–20 nm, which would be a realistic dimension for micelles. But as this method is questionable because of its susceptibility to the formation of artifacts, it cannot really also prove lidocaine micelles.

A characteristic property of surfactants is their ability to solubilize actually insoluble substances in water [15, 16], e.g., lipophilic dyes [17]. Exactly this happens to Sudanred B, a substance used in microbiology for coloring hydrophobic structures, when stirred in a solution of lidocaine HCl (Fig. 4). But the concentration of local anaesthetic necessary for a noticeable increase in dye solubility, is even as double as high as the CMC deduced from the measurement of the surface tension,

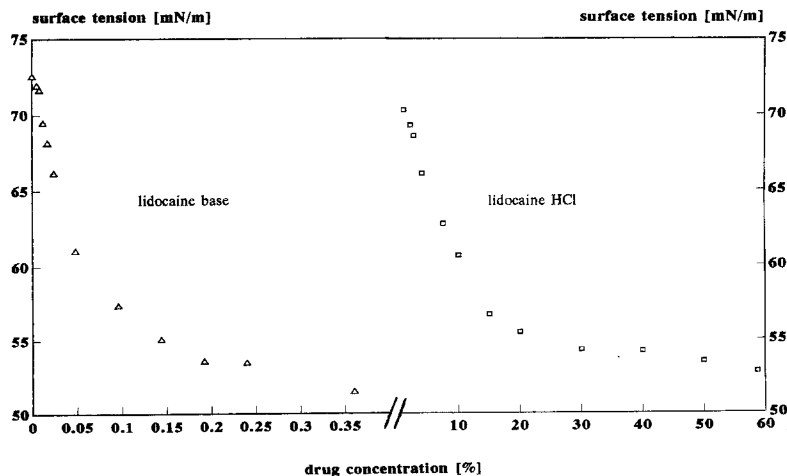

Fig. 3. Surface tension of aqueous solutions of lidocaine HCl and lidocaine base

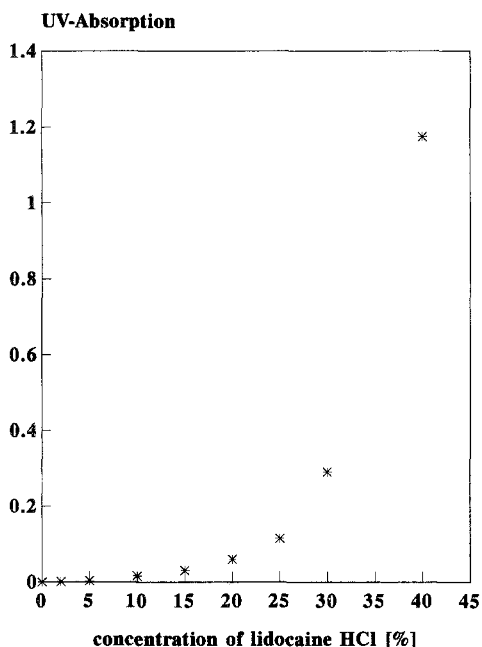

Fig. 4. Solubilization of sudanred B by lidocaine HCl in aqueous solution

although it should be at least approximately of the same order. Furthermore, the wavelength of the absorption maximum of the dye shifts with increasing concentration of the drug from 502 nm (15% lidocaine HCl) to 526 nm (40% lidocaine HCl), which is unusually much for an uptake in a micelle. The change of the solubilization site of the dye molecule in a drug micelle with increasing drug concentration would only cause a shift of a few nm [10]. Both the high concentration and the considerable maximum shift indicate that not drug associates are responsible for the solubilization of Sudanred B, but that the mechanism is an interaction between the aromatic π-complexes of drug and dye. For nicotinamide, a non self-associating aromatic compound, this mechanism is described in literature [18].

Examined by NMR spectroscopy micelle formation leads to a measurable change in the chemical shift of those atoms of a surfactant molecule which undergo an alteration in the polarity of their chemical environment [19–22]. For lidocaine HCl both ^{13}C- and ^{1}H-spectra do not show any difference in the change of the chemical shift, neither for the atoms of the aromatic part (the potential inner region of the micelle) nor for the aliphatic C_2H_5-group at the opposite end of the molecule (Figs. 5 and 6). On micellization the chemical shift of the part of the molecule forming the hydrophobic core should change discontinuously at the CMC in contrast to the chemical shift of the structures being located at the micelle water interface. This does not occur, but for both parts of the lidocaine molecule the change of the chemical shift is constantly upfield, indicating that the environment becomes more polar, which is not surprising since the concentration of a dissolved ionic substance increases from 1% to 40%. Even the amount of the change is of the same order: 0.47 ppm for the CH_3-carbon of the ethylamino-group and 0.57 ppm for the C_1 of the aromatic ring.

A further evidence for the fact that no self-association of lidocaine HCl takes place is the linear increase of the osmotic pressure of aqueous solutions in dependence of the concentration according to the values calculated for a molecular dispersion (Fig. 7). In the case of micelle formation the osmotic pressure should rise distinctly more weakly beyond the CMC as the number of osmotic effective particles is only increased by the number of micelles and not by the number of the dissolved molecules [15].

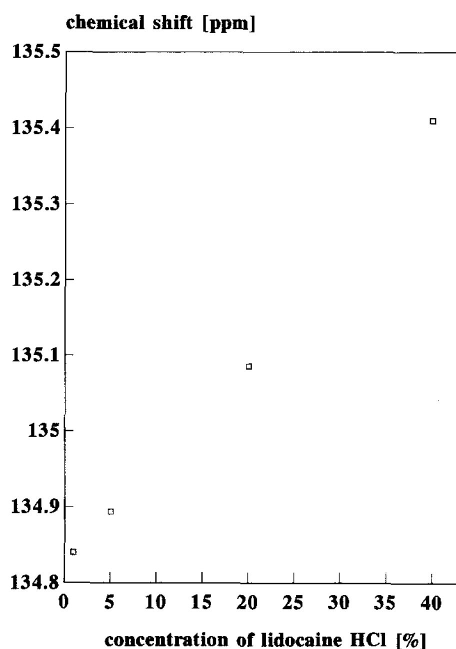

Fig. 5. ^{13}C-NMR chemical shift of C_1 of the aromatical ring of lidocaine HCl

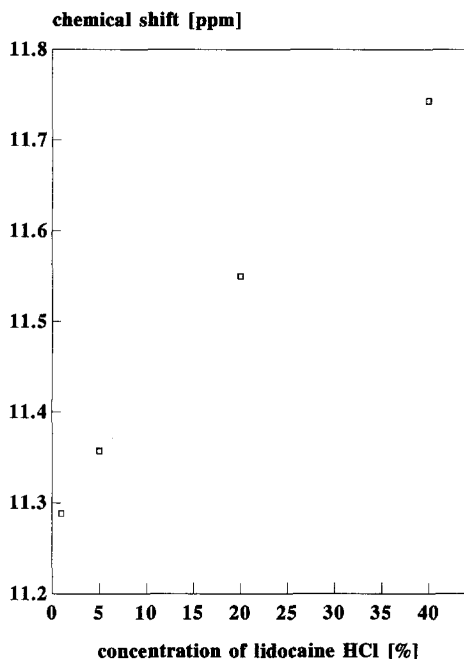

Fig. 6. ^{13}C-NMR chemical shift of the CH_3-carbon of the ethylamino group of lidocaine HCl

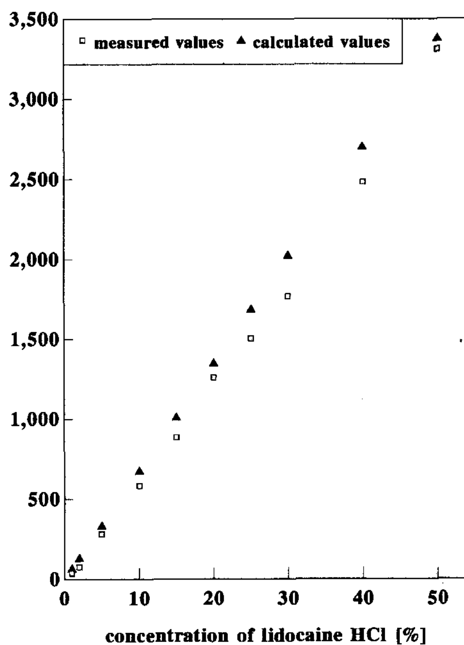

Fig. 7. Osmotic pressure of aqueous lidocaine HCl solutions

To summarize, most experiments disprove the existence of drug micelles although surface tension measurements and freeze-fracture hint at micellization. Probably the result of the measurements of the surface tension only means a saturation of the surface with drug molecules, and the freeze-fracture of the 40%-solution was an artifact produced by the preparation of a concentrated salt/water-system. So, as all the other methods indicate, self-association of the drug alone cannot play a role in the phase transformation processes mentioned above.

Colloidal-chemical phenomena in preparations containing drug and surfactant

Despite the fact that a substance does not form micelles in aqueous solution, mixed micelle formation with a "classical" surfactant can nevertheless occur. This is, for example, expressed in that way that the CMC of mixtures of both substances is decreased even below the CMC-value of the stronger surface active agent [23]. This is neither the case for mixtures of E 16 with lidocaine base nor for mixtures with lidocaine HCl, when determining the CMC from surface tension measurements (an example for such a curve is given in Fig. 8). This becomes clearly

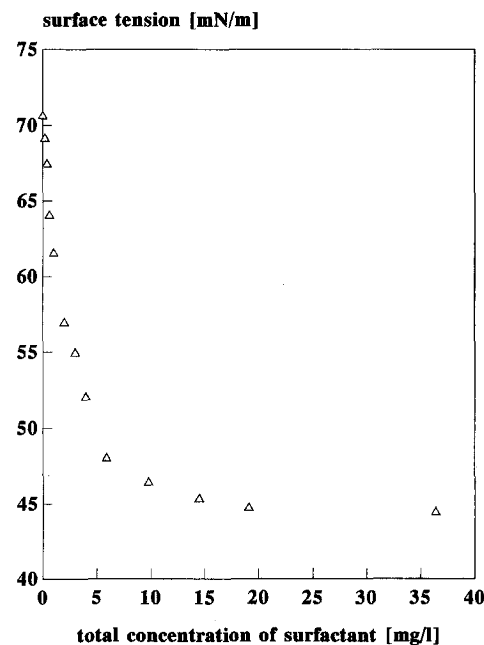

Fig. 8. Surface tension of an aqueous solution containing E 16 and lidocaine base in a ratio of 70:30

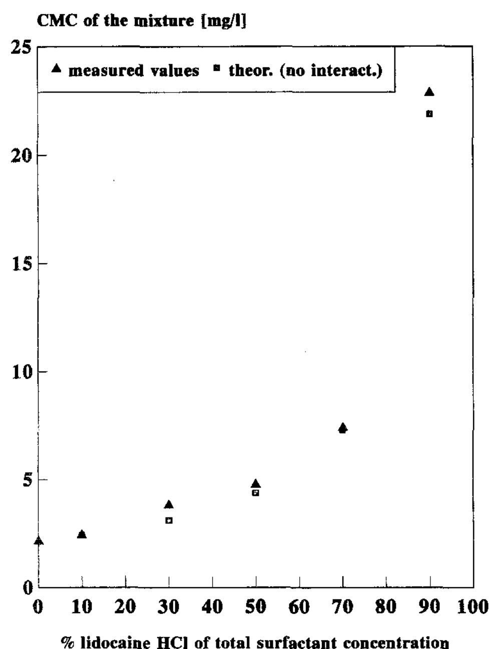

Fig. 9. CMC of mixtures of E 16 and lidocaine HCl

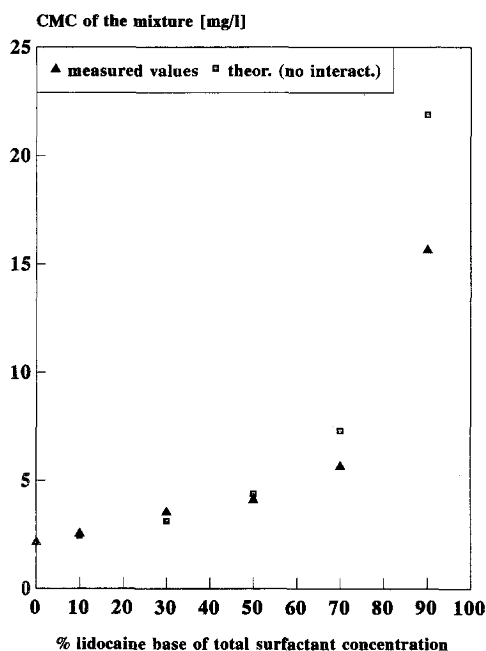

Fig. 10. CMC of mixtures of E 16 and lidocaine base

visible from Figs. 9 and 10: the CMC of the mixtures rises when part of E 16 is substituted by the drug in an extent according to the smaller amount of E 16 contained. E 16 itself exhibits a CMC of ~2 mg/l and a solution containing surfactant in the relation 10% E 16/90% drug has a CMC of ~20 mg/l. From these results it can be concluded that no mixed micelle formation of either lidocaine base and E 16 and lidocaine HCl and E 16 takes place.

Another possibility to detect mixed micelles is the gel permeation chromatography [5–7] that classifies particles according to their size. Larger particles like micelles are eluted in a shorter time as they cannot diffuse into the pores of the gel, whereas smaller molecules show greater retention times. If these smaller molecules are partly bound to the surfactant aggregates they can be detected both together with the micelles (e.g. by UV-spectroscopy) after a short time and also within a second peak after longer retention time representing the molecular dispersed fraction of the drug. Such a curve for a mixture containing lidocaine base and E 16 in the relation 1:1 (Fig. 11) shows two clearly separated fractions of surfactant (absorbing at $\lambda = 270$ nm and $\lambda = 293$ nm in a ratio of ~1.73) and drug (only absorbing at $\lambda = 270$ nm). That means that no drug molecules are eluted together with surfactant molecules after the same retention time as it should occur on the formation of mixed associates. In this case the UV-absorption after the elution of ~10 ml (first peak) at λ_{max} of the drug would have been distinctly greater than the measured values. Thereby also the GPC disproves the existence of mixed micelles of lidocaine and E 16.

An important parameter for the dynamic viscosity of surfactant solutions is the geometrical

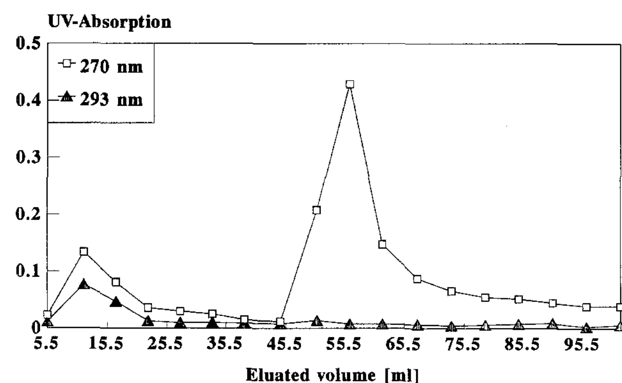

Fig. 11. GPC of an aqueous solution of E 16/lidocaine base 50/50, $c = 4$ g/l

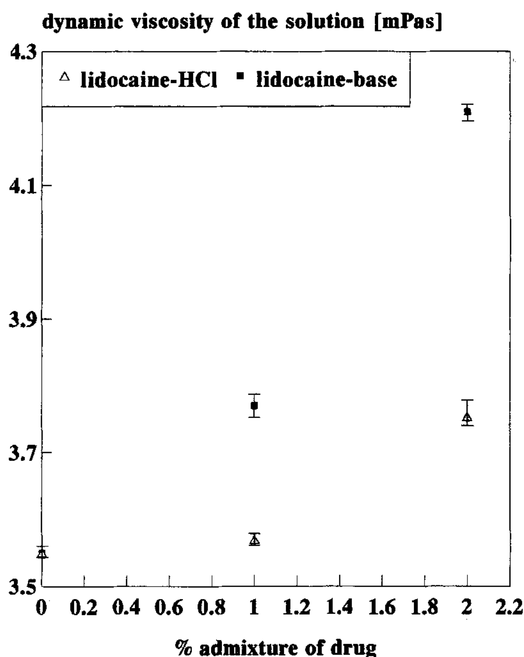

Fig. 12. Increase in dynamic viscosity of a 15% solution of E 16 on addition of lidocaine base and salt

form of the colloidal associates present [24]. Solutions of globular micelles mostly exhibit a dynamic viscosity close to the value of the pure solvent. On the other hand, anisometric particles such as rodlike micelles can give rise to an increase in dynamic viscosity by orders because of their mutual obstruction when flowing. Both GPC-experiments and measurements of the surface tension of aqueous solutions were performed in concentration regions where the base form of the drug was soluble, but if greater amounts of base and salt form are mixed with surfactant, some interesting differences can be noticed when examining the dynamic viscosity of the solutions (Fig. 12). Obviously, the salt form has a rather small influence, whereas 2% addition of the base induces an increase in viscosity from 3.55 mPas to 4.21 mPas which is nearly 20%. This is possibly caused by a change of the geometrical form of the surfactant associates to a more anisometric structure similar to an increase in surfactant concentration.

Tensiometric-CMC and GPC investigations show that neither the salt nor the base form of the drug take part in the structure of the surfactant associates, i.e., no mixed micelles are formed at low drug concentrations. Hence, in these concentration ranges a true solution is thermodynamically preferred. Also in high concentrations the salt form does not exhibit a distinct influence on the surfactant associates, which becomes obvious by the rather weak influence on the dynamic viscosity of the systems. In contrast to this, the participation of the base form in the microstructure probably leads to growth of the surfactant micelles in at least one direction, causing a noticeable change in flow behavior.

Conclusion

As in dilute aqueous solutions, the drug shows neither any tendency to self-association nor does a participation of drug molecules in the microstructure of surfactant associates take place; thus far, investigations of these systems do not permit any inference on the reasons for the observed phase transformation. Only if the concentration of the drug is increased does a measurable influence on the associate structures become evident: the viscosity of the preparations clearly rises, possibly hinting at particle growth to a more rodlike shape caused by solubilized drug molecules. In very highly concentrated surfactant systems this could cause the changing of large rodlike micelles into a liquid crystalline hexagonal structure. In any case, size, shape, and structure of these particles have to be investigated further in order to get more information about the localization of the lidocaine molecule.

Acknowledgements

The authors wish to thank the Institut für Virologie, Philipps-Universität Marburg, for the possibility of using the transmission electron microscope to examine the freeze-fractured and replicated samples.

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Received January 8, 1993;
accepted March 8, 1993

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