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Effect on the partition equilibrium of various drugs by the formation of mixed bile salt/phosphatidylcholine/fatty acid micelles A characterization by micellar affinity capillary electrophoresis. Part IV

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Abstract

Mixed micelles, which mimic the bile containing fatty acids in the gastrointestinal tract, were used as a pseudostationary phase in capillary electrophoresis. The mixed micellar system studied contained the dihydroxy bile salts sodium glycodeoxycholate or sodium taurodeoxycholate or the trihydroxy bile salt sodium taurocholate, in association with different sodium salts of fatty acids including lauric, myristic, palmitic, oleic, stearic and linoleic acid and lecithin or dipalmitoylphosphatidylcholine as phospholipid. The determination of the changing mobilities of ionic analytes in the presence of mixed micelles reflected interactions between the used drugs and the mixed micelles. These were determined as dependence on the fatty acid concentration in the bile salt/fatty acid micelles and the mixed bile salt/phosphatidylcholine/fatty acid micelles. The capacity factor, k_{mmc}, for the partition between mixed micellar and aqueous phase was calculated. The partition equilibrium of basic and acidic drugs depends considerably on shape and charge of the mixed micelles (dependent on the fatty acid concentration) as well as on the acid–base properties of the drug. The mobility of the micelle aggregates was determined as an important reference value to the calculations of k_{mmc}. This paper also describes the use of laser-induced fluorescence detection and electrospray mass spectrometry and tandem mass spectrometry for the characterization of the mixed micelle composition. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Affinity capillary electrophoresis; Micelles, mixed; Drugs; Pharmaceutical analysis; Fatty acids; Bile salts; Phosphatidylcholines

1. Introduction

It is well known that dietary fats, mainly triglycerides with long-chain fatty acids (FAs), are emulsified in the gut lumen and subsequently hydrolized by pancreatic lipase to poorly water soluble monoglycerides and FAs. These split products are solubilized by bile salts (BSs) and phosphatidylcholines (PCs) released from the gall bladder, resulting in the formation of mixed micelles.

The absorption of lipophilic drugs and all other lipids is influenced by incorporation in these micelles.

To obtain some information about the interactions

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of drugs with these BS aggregates, we investigated model systems with different concentrations of FA in the BS/PC solutions. As already pointed out in Parts I, II and III, capillary electrophoresis (CE) is a versatile tool to monitor these interactions [1–3]. Since these interactions can be described using affinity capillary electrophoresis (ACE) as well as micellar electrokinetic chromatography (MEKC), the term micellar affinity capillary electrophoresis (MACE) was used as a generic term. It has been shown, that the content of PCs in the BS/PC system have a crucial influence on the partition behaviour of the used drugs. Basic as well as acidic drugs are influenced to a different degree. Lipophilicity, structure and size have a stronger influence on the partition behaviour than the charge of the molecule.

Since the interactions of drugs are strongly dependent on the physicochemical properties of the micelles such as size, charge and shape, two different electrophoretical methods were used for the characterization of the mixed micellar phase.

Despite the intensive study on BS micellization and the ability of bile acid solutions to solubilize FAs, no satisfying information is available concerning the nature of the interactions of FAs with BS micelles and BS/PC micelles.

Sallee [4] assumed that FAs interact with micelles according to a phase distribution phenomenon so that they exist in two phases in equilibrium (in aqueous solution and in the mixed micelle). It is known, that in the case of a constant BS concentration the FA monomer activity is linear related to the total FA concentration, while the FA monomer activity is nearly constant and independent of the total concentration, when the ratio of FA to micellar BS concentration is constant. If two types of phases exist, both molecular arrangements of FAs can interact with the drug.

The addition of PCs like dipalmitoylphosphatidylcholine (DPPC) to a micellar BS solution increases the solubility of FAs enormously [5–8]. Since the cited papers do not really cover the formation of mixed BS/PC/FA micelles and the results apply to other FA concentration ranges, we investigated this topic using a different spectrum of methods including fluorescence labelling, CE–MS and partition studies with model drugs.

The present paper deals with the solubilization properties of mixed micellar BS solutions for drugs in vitro. Cationic drugs like propranolol, quinine, atenolol and etilefrin as well as nonionic (chloramphenicol) and anionic drugs (ibuprofen, diclofenac) were used as model substances. In these investigations the interactions between mixed BS/FA and BS/FA/PC micelles and various drugs have been studied. Furthermore the influence of the BS type (di- or trihydroxy) and FA species on the partition behaviour was studied.

2. Experimental

2.1. Chemicals

Propranolol·HCl, quinine·HCl, etilefrine·HCl, atenolol, chloramphenicol, ibuprofen·Na and diclofenac were purchased from COM-Pharma (Hamburg, Germany). The model samples (1 m*M*) were prepared by dissolving analytical pure substances in bidistilled water. The sodium salts of taurocholic acid (NaTC), glycodeoxycholic acid (NaGDC) and taurodeoxycholic acid (NaTDC), DL-α-phosphatidylcholine, dipalmitoyl (C16:0) (DPPC), L-α-phosphatidylcholine (lecithin) from fresh egg yolk (approx. 99%) and as FA components the sodium salts of lauric, myristic, palmitic, stearic, oleic and linoleic acid of analytical grade were obtained from Fluka (Buchs, Switzerland). 1,2-Dipalmitoyl-*sn*-glycero-3-[*N*-(7-nitro-2-1,3-benzooxadiazol-4-yl)]-phosphoethanolamine (NBDPE) was from Avanti Polar Lipids (Alabaster, AL, USA). Mixed micellar solutions were prepared by adding PC and FA to the BS solution. All systems were stirred continuously at 50°C until the solutions became clear. In the case of unsaturated FAs the stirring process was done under argon to prevent oxidation.

2.2. Capillary electrophoresis

A Hewlett-Packard (Waldbronn, Germany) $HP^{3D}CE$ system fitted with a 600 (515)×0.05 mm fused-silica capillary with extended lightpath and an on-column diode array detector (190–600 nm) were used for MACE. The capillary was preconditioned for 10 min with 1.0 *M* NaOH before the first run and then for 3 min with 0.1 *M* NaOH and 3 min with run

buffer prior to each subsequent run. The separation conditions were: voltage +30 kV (inlet), 200 mbar s pressure injection, 25°C capillary cassette temperature. The detection was done on the cathodic side at λ=200 and 220 nm, respectively. All micellar buffer solutions and samples were filtered through a membrane filter of 0.2 μm pore size and degassed by ultrasound before use. A Beckman P/ACE system 5500 (Beckman, Fullerton, CA, USA) with a laser-induced fluorescence (LIF) detection system (excitation at λ=488 nm, 530 nm emission filter) was used for measurements of the NBDPE labelled mixed micelles. The separation conditions were: +30 kV voltage (inlet), pressure injection (0.5 psi/10 s), 25°C capillary temperature.

The determination of the electroosmotic flow (EOF) was performed using Microcal Origin (see Section 3.3).

2.3. CE–MS

CE–MS results were obtained with the HP^{3D}CE system coupled to a LCQ ion trap mass spectrometer (Finnigan MAT, San Jose, CA, USA). The ionization was done by electrospray (ESI) at a voltage of 4.7 kV mainly in the negative mode. The effective separation voltage is calculated from the difference between nominal CE voltage applied to the capillary inlet and electrospray voltage applied to the outlet instead of the ground potential in normal CE experiments. Sheath liquid (methanol–water, 80:20, 0.2% triethylamine) was added by a syringe pump via a PTFE tubing.

For experiments with additional UV detection an 800 (215)×0.05 mm fused-silica capillary was used. Without UV detection, a capillary of 500 mm length was sufficient (CS, Langerwehe, Germany).

3. Results and discussion

Bile is an aqueous electrolyte solution containing up to 70% BSs, 20% lecithin and approx. 4% cholesterol. Previous papers [2,3] discussed simple BS micelles and mixed BS/PC micelles. Cholesterol showed no influence on the partition behaviour of the model drugs over the biologically occurring concentration range. Hence, it was not included in the investigations. According to its biological function, bile solubilizes the degradation products of fats from food. For this reason FAs were studied over a wide concentration range as components of binary BS/FA and ternary BS/PC/FA micelles. The interest was focused on the concentration range in which the drug mobility changed. The maximum FA concentration was limited by the individual solubility in a 20 m*M* BS solution and was dependent on the PC concentration.

3.1. BS/FA

Although a lot of quantitative data about formation, aggregation numbers, size and shape of the BS micelles as well as BS/PC mixed micelles is available [9–11], the interactions of FAs with BS micelles are not yet completely understood. The aggregation processes in physiological solutions make the FA/BS solutions very complex. Probably BSs and FAs form a mixed micelle (BS/FA, 15:1) that increases in size and charge if more FA is added. Since both are water soluble amphiphiles, they will be present in the micelles and as monomer in the aqueous solution. It is not finally cleared up if in a concentration range above the ratio 15:1 two different micellar phases exist or a new type of mixed micelle is formed [12].

The migration behaviour of a solute interacting with one or more additives was described previously [3]. Only in special cases the calculation of the partial capacity factors (k_{smc}=capacity factor for simple BS micelles, k_{mmc}=capacity factor for mixed BS micelles) is possible, e.g., if the drug shows predominantly interactions with one phase, including the aqueous phase, or if only one mixed micellar phase or nonmicellar phase exists.

In principle, only the partition of the basic drugs is influenced by the FA concentration. Obviously, in the BS/FA system the ionic interactions play a major role in terms of influencing the electrokinetic migration behaviour of the drugs. Fig. 1a shows the changes in the mobilities of the cationic drug propranolol as influenced by FA concentration (lauric and oleic acid) at a constant BS concentration (NaGDC and NaTDC). With an increase of the FA concentration in the CE electrolyte at a constant BS concentration, an increase of the negative net mobili-

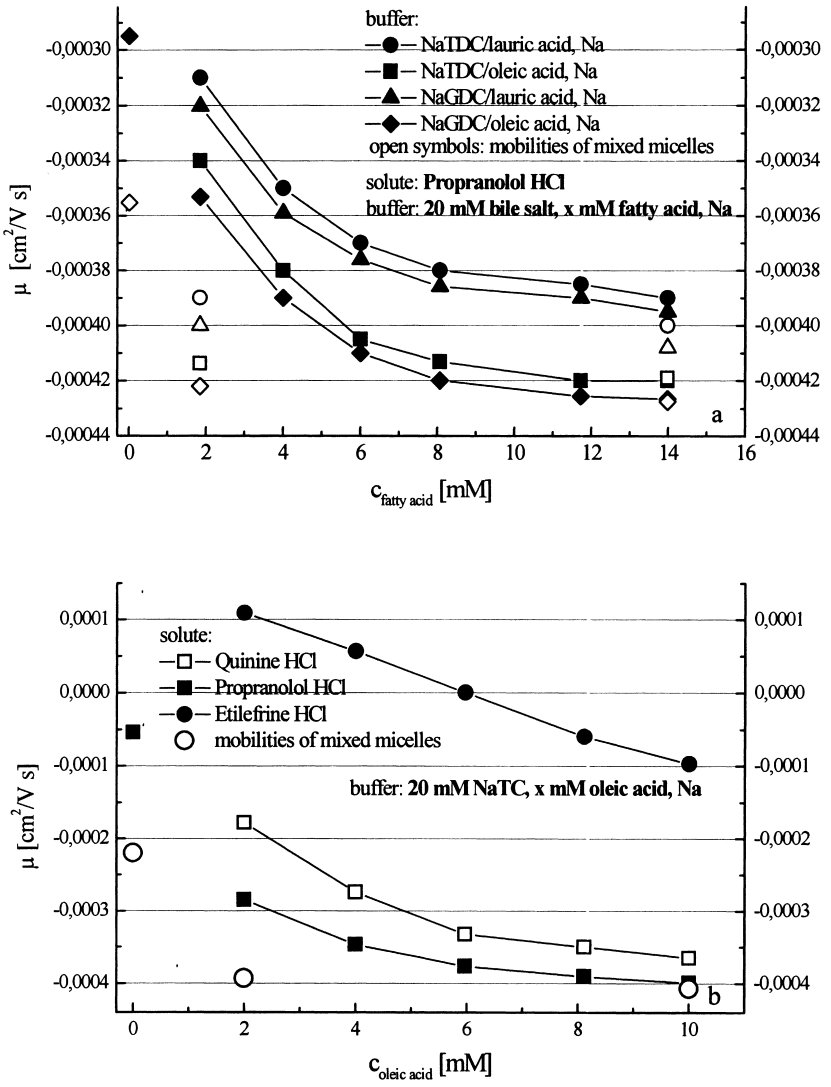

Fig. 1. Electrophoretic ion mobility μ ($cm^2/V\,s$) of basic drugs as influenced by FA concentration. Comparison between (a) lauric and oleic acid as well as NaGDC and NaTDC and (b) different drugs in the presence of NaTC and oleic acid (buffer: 20 m*M* NaTC, *x* m*M* FA, 20 m*M* phosphate, pH 7.4; UV detection λ=220 nm).

ty was observed. The reason for the clearly increased mobility of propranolol above 1.4 m*M* FA is a clearly increased affinity to the mixed micellar phase. Due to the incorporation of more than one FA molecule into a micelle the structure and properties seem to change, so that the solubilization ability particularly for cationic drugs is improved. The absolute change of the net mobility is independent of the type of FA (chain length and number of unsaturated bonds) as well as of the conjugation of the BS. Only slight mobility differences were observed between systems with NaGDC and such with NaTDC. The reason for this behaviour is the similarity of the mixed micelle mobilities as well as of the drug affinities to both BS types. Up to 1.4 m*M* FA only one FA molecule is incorporated into the micelle, while the aggregation number of a simple NaGDC micelle is 12–14. The difference $\mu-\mu_{mmc}$ was not

smaller if the FA concentration is below 2 m*M* (μ=measured mobility of drug based on the BS, PC and FA concentration in the run buffer, μ_{mmc}= mobility of mixed micelle). Above this concentration, the mobility of the mixed micelles μ_{mmc} keeps constant, but the negative net mobility of propranolol is increased with FA concentration, so that $\mu-\mu_{mmc}$ decreases. The determination of ionic mobilities of the mixed micelles is described in Section 3.3.1.

In the presence of NaTC a change of μ by increasing the oleic acid concentration was also observed. Fig. 1b shows a comparison between lipophilic (propranolol and quinine) and hydrophilic (etilefrine) drugs. Since the capacity factor of propranolol for simple NaGDC micelles [k_{smc} for 20 m*M* NaGDC=7.4, with $k_{smc}=n_{smc}/n_{aq}=(\mu_D-\mu)/(\mu-\mu_{smc})$; μ_D=mobility of drug in aqueous solution, μ_{smc}=mobility of simple BS micelles] is greater than for simple NaTC micelles (k_{smc} for 20 m*M* NaTC=1.2) [1], the absolute change of the net mobility of propranolol in the presence of NaTC and with increasing oleic acid concentration has to be clearly greater than the change of mobility in the presence of NaGDC (Fig. 1a). The partition equilibria result from the differences between drug mobilities and the mobility of the mixed micelles.

The calculation of the capacity factors k_{mmc} is only possible if the number of phases and their electrophoretical properties are known. Several observations indicate, that NBDPE labels exclusively the mixed micellar phase (see Section 3.3).

Only one main peak is observed by LIF detection of NBDPE. Theoretically this is even possible in the presence of several micellar phases, when NBDPE is distributed very quickly. Since pure FA micelles cannot be labelled under the given conditions, the LIF peak corresponds to the mixed micelle, even if a rapid exchange of FA molecules between mixed and pure FA micelles is taking place. Furthermore, it was shown that above 14 m*M* oleic acid propranolol and quinine migrate with the same velocity as the mixed micelle (corresponding to μ_{mmc}). This indicates that both substances are completely solubilized in the mixed micellar phase. If pure FA micelles would exist, the affinity of the drugs to them must be very low. Independent of the BS type (NaGDC or NaTC), μ_D of propranolol is above 10 m*M* oleic or linoleic acid identical to μ_{mmc} labelled by NBDPE.

In the case of NaTC/lauric acid no reproducible results could be achieved. Obviously no stable mixed micelles are formed under these conditions (see Section 3.3).

3.2. BS/PC/FA

Fig. 2a shows the mobility of various drugs as influenced by oleic acid at constant NaGDC in the presence of 5 m*M* DPPC. Again only the basic drugs are influenced by the FA concentration in the mixed solution. The net mobilities of the anionic drugs ibuprofen and diclofenac kept constant when the FA concentration was increased. For the hydrophilic drugs atenolol and etilefrin a drastic change was observed. Above 8 m*M* oleic acid and in the presence of 5 m*M* DPPC or 4.5 mg/ml lecithin, propranolol and quinine migrate with the same ionic mobility, because they are both completely solubilized in the mixed micellar phase (Fig. 2a,b).

Fig. 2b shows a comparison between two typical electropherograms of the binary system BS/lecithin and the ternary system BS/lecithin/FA. At the top it is shown that the cationic drugs propranolol and quinine are separated, both are shifted significantly. The less lipophilic atenolol and etilefrine show a much smaller shift. At the bottom it is shown that the addition of FAs causes a significant change in migration times and ionic mobilities of atenolol and etilefrine while the values of quinine and propranolol stay constant. The concentration of 4.5 mg/ml lecithin is equivalent to a DPPC concentration of 5 m*M* (μ_D for 20 m*M* NaGDC, 5 m*M* DPPC is equal to μ_D for 20 m*M* NaGDC, 4.5 mg/ml lecithin).

The maximum shift ($4.00\cdot10^{-4}$ cm^2/V s) of propranolol and quinine is limited by the mobility of the mixed micelles. Above 10 m*M* FA the electrophoretical properties of the mixed micelles in presence of NaGDC showed no further change. This mobility is characteristic for the system NaGDC/PC/FA and corresponds to the maximum shift of propranolol and quinine. Although it seems possible, that in addition to the described mixed micelles other FA aggregates exist, these do not influence the drug mobilities and were therefore not subjected to further investigation.

In contrast, atenolol and etilefrine show a change

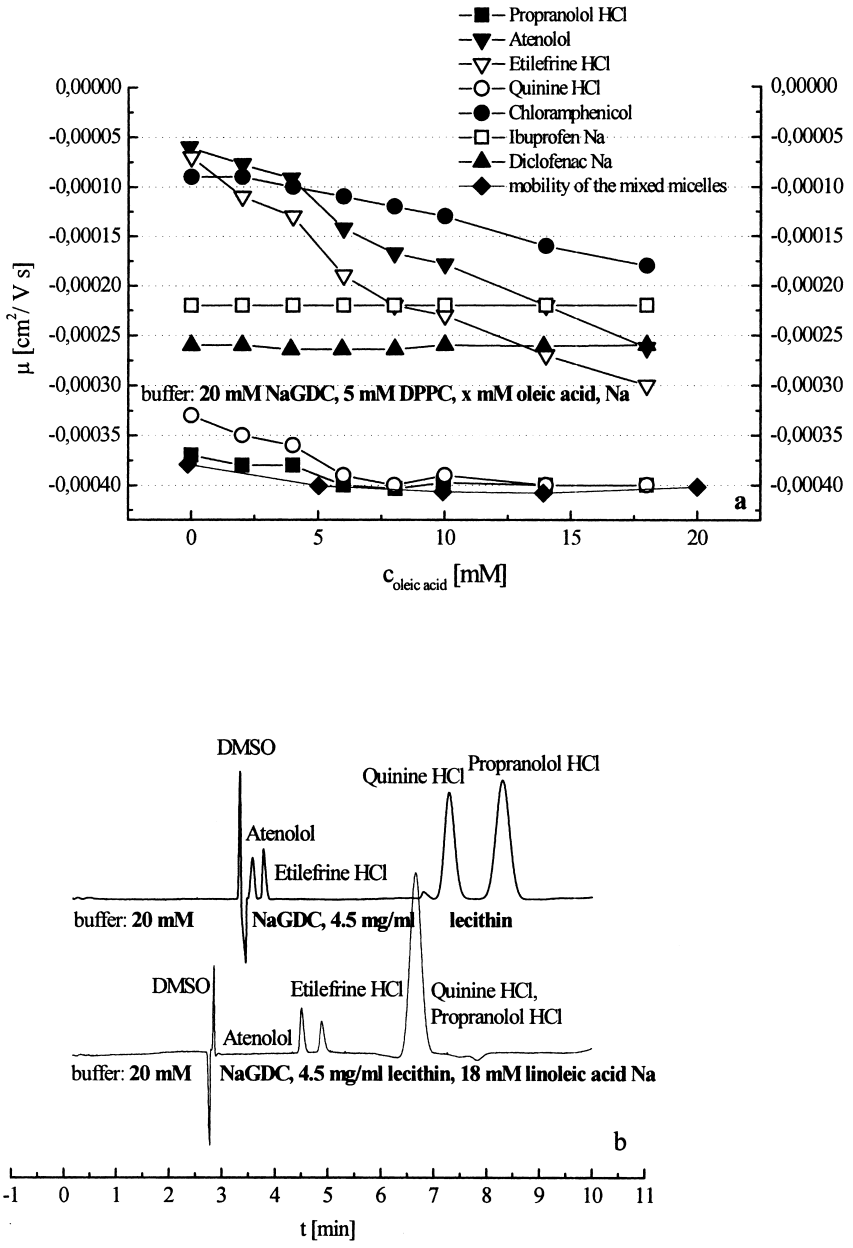

Fig. 2. (a) Electrophoretic ion mobility μ ($cm^2/V\ s$) of different drugs under the influence of oleic acid in the presence of DPPC and NaGDC. (b) Electropherogram of propranolol, quinine, atenolol and etilefrine dependence on the linoleic acid concentration in the presence of lecithin (buffer: 20 m*M* NaGDC, 5 m*M* DPPC or 4.5 mg/ml lecithin and *x* m*M* FA, 20 m*M* phosphate, pH 7.4, UV detection λ=220 nm).

in the net mobilities and a maximum shift which depends on the type of the FA (chain length/presence of double bonds) (Fig. 3). While the affinity of these drugs to pure BS and BS/PC micelles is low, the influence of the FA concentration becomes obvious and can be studied very well.

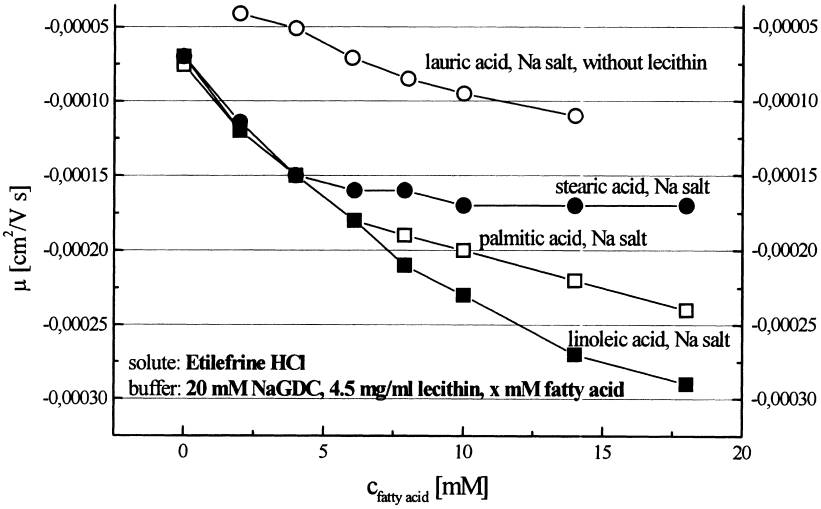

Fig. 3. Electrophoretic ion mobility μ ($cm^2/V\,s$) of etilefrine as influenced by various FAs with and without lecithin in the buffer (buffer: 20 m*M* NaGDC and 4.5 mg/ml lecithin, *x* m*M* FA, 20 m*M* phosphate, pH 7.4; UV detection λ=220 nm).

Since the more lipophilic drugs propranolol and quinine are completely solubilized in the mixed micelles even at low PC concentrations, the addition of FAs does not cause major changes. This case illustrates the limitations of the affinity chromatography. If the differences between solute and interacting agent are small, the estimation of the interactions becomes less sensitive.

The following relation was found concerning the shift of μ_D for etilefrine and atenolol in aqueous solutions containing BSs, PC and FAs: linoleic≈oleic>palmitic≈lauric≈myristic>stearic acid. If phospholipids are absent, the change as well as the maximum shift of the ionic mobility of etilefrine is much lower when the FA concentration was increased.

Obviously the presence of double bonds in the FA chain is important. Probably, the angular structure caused by the *cis* double bonds leads to a decreased packing density at the surface of the mixed micelles and thereby to an increased micelle radius compared to micelles with saturated FAs. In a preliminary work it was shown that the interactions strongly depend on the micelle size [2]. The weak interactions of drugs to stearic acid mixed micelles result from its lower solubility in the media used.

The mobilities of the anionic drugs ibuprofen and diclofenac were not influenced by FAs, indicating that their solubility is not increased, probably due to electrostatic repulsion.

3.3. Characterization of the micellar phase

The mobility of the mixed micelles has to be known for calculating capacity factors. Two different methods were applied in order to characterize the electrophoretical properties of the mixed micellar phases.

3.3.1. Method 1

The mixed micelles were labelled with the fluorescing phospholipid derivative NBDPE to determine the ionic mobility by means of the very sensitive LIF detection. It can be assumed that the highly lipophilic NBDPE molecules are rapidly distributed between the mixed micelles [13]. Very sensitive LIF was used instead of UV detection as we wished to use NBDPE concentrations as low as possible. Below 1 m*M* NBDPE UV absorbance was too weak, above that concentration μ_{mmc} was falsified intolerably. The anionic NBDPE is completely incorporated in the mixed micelles (see Section 3.3.2) [3]. A possible alternative to LIF detection would be the use of a UV high-sensitivity cell, commercially available from Hewlett-Packard.

The direct determination of EOF was not possible

because of the lack of a nonionic fluorescence marker which shows no interactions with the micelles. Therefore a preliminary run under the same conditions was performed. After the injection of a 10% dimethyl sulfoxide (DMSO) solution a typical current curve (with a step at the time when DMSO was leaving the capillary) is observed. For a more exact evaluation the curve was treated as a function and the peak maximum of the first derivation provided the time of EOF.

The measurements have shown that the addition of FAs to simple BS micelles and to the mixed BS/PC micelles remarkably influences the mobility of the labelled mixed micelles. Since pure FA aggregates are not detectable, no suggestion about them could be given. Fig. 4 shows typical electropherograms. If pure BS micelles are used, two peaks are detected. The addition of DPPC causes a visible enlargement of the peak, while the mobility changes only slightly. In presence of FAs, the mobility of the detected mixed micelle increases and the peak becomes broader, which is probably caused by an increased longitudinal diffusion (longer migration times) and by an increase in polydispersity. Between 2 and 18 m*M* FA in buffer as well as in sample the mobilities remain constant. Several nonreproducible peaks were detected in the system NaTC/lauric acid. Obviously no homogenous and stable mixed micelles were formed.

3.3.2. Method 2

The aim of using CE–MS was not to determine the mobility of the mixed micellar phase, but to examine the micelle composition. The experimental conditions are not completely transferable, because high concentrations of surfactants are very detrimental to ESI performance.

In CE–MS experiments it could be shown that in binary (e.g., NaGDC/oleic acid) as well as in ternary mixtures (e.g., NaGDC/DPPC/oleic acid, see Fig. 5) all substances migrate with the same velocity, implying that they are in one phase. To be exact, this statement has to be qualified with respect to the detection limit of CE–MS.

Additional tandem mass spectrometry (MS–MS) and MS^3 experiments were performed to elucidate the structure of the different occurring adducts which was necessary for a reliable identification. The

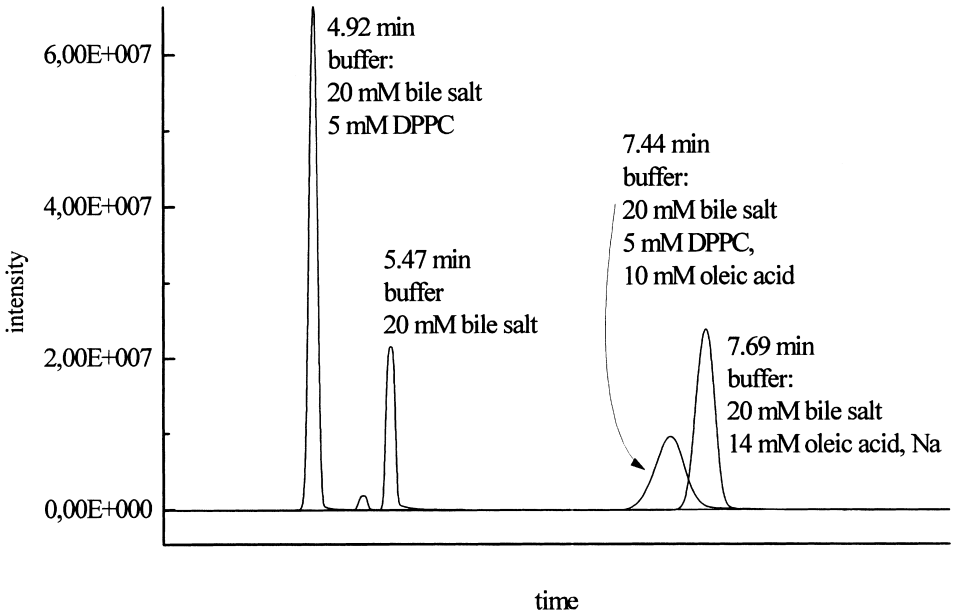

Fig. 4. Typical electropherograms of NBDPE solubilized by BS, DPPC and oleic acid, (buffer: 20 m*M* NaGDC, 0–5 m*M* DPPC, 0–14 m*M* oleic acid, 20 m*M* phosphate, pH 7.4, solute: the same content of NaGDC, DPPC and oleic acid as in the buffer, additionally $1 \cdot 10^{-5}$ m*M* NBDPE; LIF detection: λ_{ex}=488 nm, λ_{em}=530 nm).

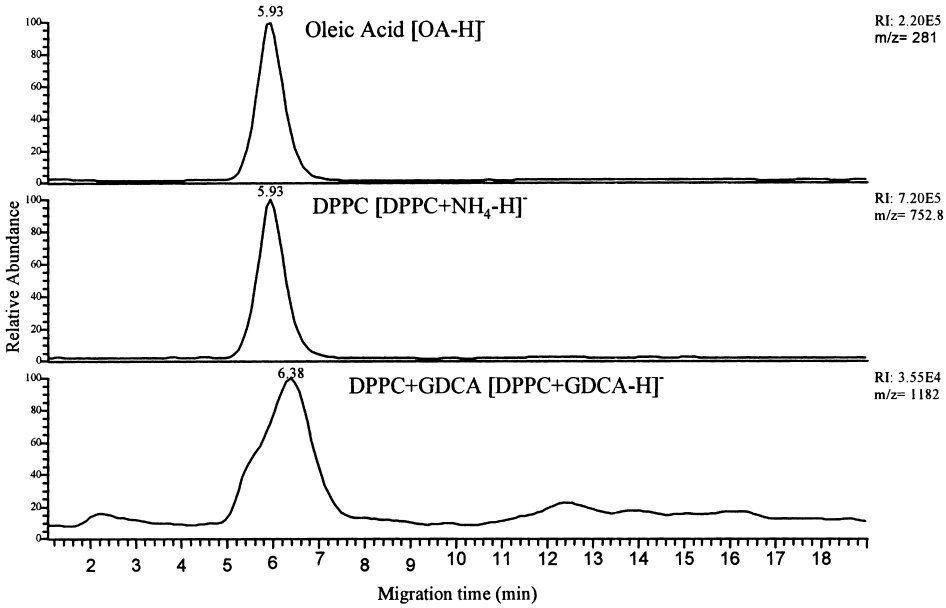

Fig. 5. CE–MS characterization of a ternary mixed micelle. The CE buffer contained 20 m*M* NaGDC and 20 m*M* ammonium acetate, while the sample was 20 m*M* NaGDC, 5 m*M* DPPC and 10 m*M* oleic acid. The m/z ranges represent the most intensive adducts. The ionization was done in negative ESI mode with selected ion monitoring detection. RI=Relative intensity.

fragmentation was performed by isolating the parent ions (peak width $m/z=2.00$) and applying mass analyzer collision induced dissociation (15–30% relative collision energy).

3.4. Capacity factor

The calculation of the capacity factors was based on the mobilities of the mixed micelles which were received by LIF detection of the NBDPE label.

3.4.1. BS/FA

No changes of the capacity factor were found for all of the model drugs in the range between 0–1.3 m*M* FA, in which one molecule FA per micelle is solubilized. Only above 2 m*M* a major increase was recorded. The greatest effect on the partition behaviour of propranolol was found for the binary mixture NaGDC/oleic acid (Table 1).

3.4.2. BS/PC/FA

Apart from the anionic drugs ibuprofen and diclofenac, the capacity factor is clearly increased by FAs. Independent of the FA dissolved in NaGDC, the drugs propranolol and quinine are completely solubilized above 8 m*M* ($k=\infty$) in the micellar phase (Table 2). For NaTC, the capacity factor is similar starting with a FA concentration of 14 m*M* with oleic and linoleic acid. The affinity of atenolol and etilefrin to the micellar phase is greater if unsaturated FAs are used.

In the case of drugs with a strong affinity to pure BS micelles (propranolol, quinine) shows the type of BS up to 10 m*M* FA concentration a significant influence. NaGDC causes a stronger shift of the partition equilibrium towards the micellar phase compared to NaTC. The influence of the BS type becomes less important during the increase of the lipid concentration. It was evident, that, in the case of drugs having weaker interactions with pure BS micelles, the type of the used BS did not influence the capacity factors over the whole FA concentration range.

4. Conclusion

The formation of mixed micelles within the ter-

Table 1
Calculated capacity factors k_{smc} for the simple BS micelles and k_{mmc} of two model drugs [conditions are described in Fig. 1a,b, $k_{mmc}=n_{mmc}/n_{aq}$=molar ratio of drug between mixed micellar phase (mmc) and aqueous phase (aq)].

BS/FA	BS/FA ratio (m*M*)	k_{smc} or k_{mnc}, propranolol·HCl	k_{smc} or k_{mnc}, etilefrine·HCl
NaGDC/lauric acid	20:0	7.4	0.7
	20:2	8.0	0.7
	20:10	26.0	1.0
NaGDC/oleic acid	20:2	8.0	0.7
	20:10	101.0	1.7
NaTC/oleic acid	20:0	1.2	0.2
	20:2	2.1	0.3
	20:10	25.0	1.0

Table 2
Calculated capacity factors k_{smc} and k_{mmc} of various drugs [conditions are described in Fig. 2a,b, $k_{mmc}=n_{mmc}/n_{aq}$=molar ratio of drug between mixed micellar phase (mmc) and aqueous phase (aq)]

NaGDC/DPPC/FA	Without PC/FA; 20:0:0 m*M*	Lauric acid, Na; 20:5:20 m*M*	Oleic acid, Na; 20:5:20 m*M*
Propranolol·HCl	7.4	∞	∞
Atenolol	0.6	1.9	3.0
Etilefrine·HCl	0.7	2.8	5.2
Quinine·HCl	5.4	∞	∞
Chloramphenicol	0.15	0.6	0.8
Ibuprofen·Na	0.0	0.05	0.05
Diclofenac·Na	0.15	0.3	0.3

nary system BS/PC/FA (20:5–10:2–20 m*M*) causes a remarkable amplification of the effects on the partition behaviour of the used drugs. The presence of BS/PC strongly increases the uptake capacity of the FAs into the mixed micelle and thus the solubility of drugs into the mixed micelle. This effect is clearly visible in the cases of etilefrine and atenolol which normally show only weak interactions. Quinine also shows a different behaviour compared to the BS/FA system.

For the hydrophilic drugs etilefrine and atenolol the capacity factors are strongly influenced by the type of FA, especially the presence or absence of unsaturated bonds appears to play a key role. The highest affinity to all FA mixed micelles was found for the cationic but relatively hydrophobic drugs propranolol and quinine. For drugs which show strong or average affinity to pure BSs micelles, up to a FA concentration of 8 m*M*, the type of BS plays the predominant role. Dihydroxy BSs (NaGDC) cause a greater shift of the partition equilibrium in the direction of the micellar phase compared to trihydroxy BSs (NaTC). An increase of the total lipid (PC and FA) concentration decreases the influence of the BS type. The BSs stabilize the mixed micelles.

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