Catanionic Drug–Surfactant Mixtures: Phase Behavior and Sustained Release from Gels

Tobias Bramer,[1] Mattias Paulsson,[1] Katarina Edwards,[2] and Katarina Edsman[1,3]

Received January 14, 2003; accepted June 30, 2003

Purpose. To study mixtures of SDS and the drugs diphenhydramine, tetracaine, and amitriptyline to compile phase diagrams and to investigate the use of interesting phases for sustained release from gels.
Methods. Phase diagrams were composed by studying large numbers of different compositions of negatively charged SDS and positively charged drug compounds visually, rheologically, and by cryo–transmission electron microscopy. Drug release from Carbopol 940 and agar gels containing interesting phases, e.g., vesicle and branched micelle phases, was measured *in vitro* by the USP paddle method.
Results. Vesicles and elongated and branched micelles were formed on the SDS-rich side in all three systems examined. The tetracaine system differed from the other two in that it showed a vesicle area in the drug-rich side. Release of diphenhydramine from Carbopol 940 gels was slowed by at least a factor of 10 when in the form of vesicles or branched micelles. The same delay was found for both drug-rich and SDS-rich tetracaine vesicles.
Conclusions. Mixtures of SDS and positively charged drugs form the same interesting phases as traditional catanionic mixtures. This may prove useful in obtaining functional controlled-release systems when using gels as drug carriers.

KEY WORDS: catanionic mixtures; surfactant; gel; slow-release; phase diagram.

INTRODUCTION

Aqueous mixtures of cationic and anionic surfactants show novel properties compared with those of the single surfactant, and interesting phases and aggregates are often formed. Equimolar mixtures of two oppositely charged surfactants with no inorganic counterions are called "ion pair amphiphiles" (IPA) (1) or catanionic surfactants (2). Mixtures of cationic/anionic surfactants, both equimolar and nonequimolar, also containing inorganic counterions are referred to as catanionic mixtures (2).

In 1989, Kaler *et al.* showed that vesicles are spontaneously formed in catanionic mixtures (3). They can be formed from a wide range of surfactant mixtures (4). Branched micelles and other phases have also been found (4–6). Several factors affect the vesicle formation. Both electrostatic interactions between the head groups and chain-packing considerations for the hydrophobic tails of the surfactants in the bilayer core determine the effective packing parameter (7). Asymmetry in the tail chain length favors vesicle formation in compositions rich in the shorter chain (8). Whereas several studies have examined the properties of a variety of catanionic mixtures, little is known of the effects of having a drug substance as one of the surfactants.

Gel formulations with suitable rheologic properties have been shown to increase the contact time with the mucosa at the site of absorption (9–12). The increased contact time of gels is caused by the mucoadhesive properties of the polymer in addition to the rheologic properties of the formulation, which will obstruct the clearance by mucosal protective mechanisms. A long residence time, however, would be advantageous only if the drug remains in the formulation and is released throughout this time. There are several ways to sustain the release from gels in order to take full advantage of the contact time, one of which applies to catanionic mixtures.

Catanionic mixtures in which a charged drug compound constitutes one of the surfactants have been shown to form interesting surfactant aggregates such as vesicles and micelles when mixed in certain ratios. These aggregates can be used as vehicles for controlled delivery of drugs from gels (13) and have been evaluated for nasal drug delivery. Aqueous mixtures of drug and surfactant yield complex multicomponent systems, depending on the counterions as well. In this study, however, a simplified ternary diagram is used, as are frequently found in the literature (3,6,14). In this study phase diagrams of mixtures of SDS and either diphenhydramine or tetracaine are examined visually, rheologically, and with cryogenic transmission electron microscopy (cryo-TEM) with the purpose of finding phases that can be used in drug delivery, e.g., vesicles and mixed micelles. Furthermore, the effect when the aggregates are added to gels is studied, as well as the effects of pH, ionic strength, and temperature. This study also evaluates the pharmaceutical use of the catanionic drug surfactant mixtures as drug delivery vehicles by studying the drug release from gels.

METHODS AND MATERIALS

Materials

Diphenhydramine hydrochloride, tetracaine hydrochloride, amitriptyline hydrochloride, and sodium dodecyl sulfate (SDS) were purchased from Sigma Chemical Co. (St. Louis, MO, USA). See Fig. 1 and Table 1 for drug characteristics.

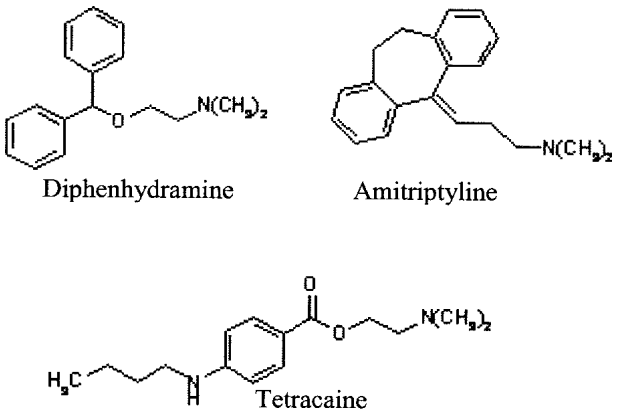

Fig. 1. Structures of drug compounds.

[1] Department of Pharmacy, Uppsala University, SE-751 23 Uppsala, Sweden.
[2] Department of Physical Chemistry, Uppsala University, SE-751 21 Uppsala, Sweden.
[3] To whom correspondence should be addressed. (email: katarina.edsman@farmaci.uu.se)

0724-8741/03/1000-1661/0 © 2003 Plenum Publishing Corporation

Table I. Physicochemical Properties of Drug Compounds, All in the Form of Hydrochlorides

Substance	pK_a	log P	CMC (mM)*	Log D
Diphenhydramine	9.0	3.11	105	1.93
Tetracaine	8.5	0.2	75	1.89
Amitriptyline	9.4	2.18	25	2.55

* Determined in 0.9% NaCl.

Poly(acrylic acid) with the proprietary name Carbopol 940 NF (C940) was a gift from BF Goodrich (Brecksville, OH, USA). Agar-agar was purchased from Merck (Darmstadt, Germany). All other chemicals were from Sigma Chemical Co. and were of analytic grade or "Ultra" quality. Ultrapure water, prepared using a MilliQ Water Purification System (Millipore, France), was used in all preparations.

Determination of Critical Micelle Concentration (CMC)

Solutions of diphenhydramine hydrochloride, tetracaine hydrochloride, and amitriptyline hydrochloride were made in 0.9% NaCl, and their CMCs were determined at room temperature (deriving from measured surface tension) using the drop-weight technique. Details of the method are described elsewhere (15).

Determination of Phase Diagrams

For all phase diagrams, 0.9% sodium chloride was used as the "water phase." Ten different compositions of the cationic drugs and the anionic SDS, with concentrations from 0 to 300 mM each with a total sum of 300 mM, were made by weighing. Each of the samples was then divided into 10 new samples, each of which had been diluted to a different concentration. In addition, solutions of drug compounds were diluted, using a 10% SDS solution. In this way new compositions were made diagonally through the phase diagram. Interesting areas were studied further by preparing more samples in these areas. The samples were examined visually, and some were also rheologically characterized and examined using cryo-TEM.

Total concentrations of drug compound and SDS of up to 100 mM (corresponding to 2.9%) for tetracaine and 300 mM (corresponding to 8.7%) for diphenhydramine were used. Higher concentrations were neglected because they were not considered to be pharmaceutically relevant.

Cryo-TEM was performed at least 10 days after preparation of the samples in order to allow the samples to age and thus reduce effects on, e.g., the vesicle size arising from differences in effects of mixing (6).

Cryogenic Transmission Electron Microscopy

Cryogenic transmission electron microscopy (cryo-TEM) was used to characterize drug–surfactant aggregates both in polymer-free solutions and in gels. A small drop of the sample was deposited on a grid covered by a polymer film, the excess liquid was blotted with filter paper, and the remaining sample on the grid was vitrified in liquid ethane. The films were transferred to a Zeiss EM 902 transmission electron microscope and kept below –165°C during the viewing process. All observations were made in the zero-loss bright-field mode at an accelerating voltage of 80 kV. Details of the method can be found elsewhere (16).

Rheologic Measurements

The rheologic measurements were carried out using a Bohlin VOR Rheometer (Bohlin Reologi, Lund, Sweden), a controlled-rate instrument of the couette type (17). All measurements were performed at 37°C using a concentric cylinder measuring system (C14). Strain sweep measurements were made for all samples to find the linear viscoelastic regions. Dynamic oscillation was performed within the linear viscoelastic region, and for the viscosity measurements suitable delay times were used to account for time-dependent viscosity.

Preparation of Gels

Carbopol gels were made by dispersing the polymer powder in 0.9% NaCl solutions containing the dissolved drug and surfactant. The dispersions were then stirred using magnetic stirring bars for approximately 1 h at room temperature, and eventually 1 M or 2 M NaOH, depending on the polymer concentration, was added to neutralize each sample to approximately pH 7. For some gels (footnote in Table II), the catanionic solutions were prepared and then mixed in the ratio 1:1 with neutralized gel. All gels were allowed to equilibrate for at least 16 h at room temperature. The pH of the gels was then adjusted to pH 7.3–7.5, 0.9% NaCl solution was added to achieve the final volume, and the gels were left for at least 90 min before measurements commenced.

One of the released gels was prepared as above, but the pH in the gel was adjusted to 11.7 to study the release of a 14 mM diphenhydramine and a 26 mM SDS solution where the pH was set above the p*K*a of diphenhydramine.

Agar gels were prepared by dispersing the polysaccharide powder in 0.9% NaCl solutions containing the drug and surfactant, and then the samples were stirred and heated at 100°C for 20 min using water baths.

Drug Release Measurements

Drug release from the gels was measured by the USP paddle method with three measurements on each sample. The gels were put in gel containers with a fixed volume of 6 cm^3 and a surface area of 21 cm^2, covered by a coarse mesh-size plastic net and a stainless steel net. The gel containers were immersed in 250–750 mL of 0.9% NaCl solution, stirred at 20 rpm, and maintained at 35°C using a Pharma Test PTW II USP bath (Pharma Test Apparatebau, Germany). The release of the pH 11.7 gel was, however, performed in a pH-adjusted 0.9% NaCl solution at pH 11.7. The medium volume was chosen to give a suitable spectrophotometric signal, and the stirring rate was chosen so that it would give adequate convection and minimize surface erosion of the gels.

On-line measurements of the concentration were performed by continuously flowing the dissolution medium through a UV-vis spectrophotometer (Shimadzu UV-1601, Shimadzu, Kyoto, Japan) using a peristaltic pump and ismaprene tubing (Ismatec SA, Zürich, Switzerland). The absorbance was measured every 150 s for the first 45 min, then at 65 min, and eventually every 30 min until the last measurement was made 9 h after the first one. The wavelengths used

for UV absorbance detection were based on the maximum absorbance of each substance: 258 nm for diphenhydramine and 310 nm for tetracaine.

If the drug release is diffusion controlled, the factor n in Eq. (1) should have a value of 0.5:

$$\frac{M_t}{M_\infty} = kt^n \tag{1}$$

where M_t is the amount released at the time t, M_∞ is the amount released at infinite time, t is the time elapsed since the experiment started, and k and n are proportionality factors.

Under sink conditions during the initial part of the release, one-dimensional Fickian diffusion from a gel holder can be expressed by:

$$Q = 2C_0\left(\frac{Dt}{\pi}\right)^{1/2} \tag{2}$$

where Q is the amount of drug released per unit area, C_0 is the initial concentration of the drug in the gel, D is the diffusion coefficient of the drug in the gel, and t is the time elapsed since the release experiment started. The equation is valid for the first 60% of the fractional release (18,19). Plots of the initial drug release vs. the square root of time should, according to Eq. (1), give a straight line, and the diffusion coefficient can be calculated from the slope of that line. Diffusion coefficients were calculated for the first 40 min of release for each sample. In our laboratory setting the gel was placed in a confined space and was not allowed to swell during the study. After approximately 3 h the spectrophotometer also starts to detect significant amounts of light scattering from polymer released in the medium. This contributes to a false-positive effect on the fraction released, and in the last point of the measurement the fraction released is higher than the theoretical unity. This is further discussed by Paulsson and Edsman (20). Because the drug diffusion coefficient is calculated from the initial 40 min of release, there is no interference from the polymer light scattering.

Statistical Analysis

The diffusion coefficients were statistically analyzed, using ANOVA and Bonferroni's multiple-comparison test as *post hoc* test, where $p < 0.05$ was considered to be statistically significant and the standard deviation (SD) is given for each group of samples.

Miscellaneous

The salt and pH dependence were examined in a solution containing diphenhydramine vesicles. A solution of 120 mM diphenhydramine and 180 mM SDS was visually examined at pHs between 0.5 and 11, where the samples were allowed to equilibrate for at least 6 weeks. To study the salt dependence of the vesicle solution, the pH was adjusted with NaOH to 7.45, and NaCl was added from 0.9% to 5.4% w/w.

RESULTS AND DISCUSSION

Phase Behavior

The physicochemical properties of the three drug substances used in this study are shown in Table I. The drugs were selected with respect to their CMCs and log p values to represent a variety of drugs. No CMC could be detected for the most hydrophilic drug, tetracaine. The most lipophilic compound, amitriptyline, had the lowest CMC of the three drug compounds studied. The phase behavior of aqueous mixtures of diphenhydramine-SDS and tetracaine-SDS at room temperature can be seen in the phase diagrams in Fig. 2. Both vesicles and micelles were found, as well as heterogeneous two-phase regions and precipitations.

Vesicles

On the SDS-rich side, large vesicle regions can be seen for both diphenhydramine and tetracaine mixtures. In Fig 3a, a cryo-TEM picture is shown of spherical and fairly monodisperse vesicles of tetracaine on the SDS-rich side. Tetracaine vesicles seem to exist with both positive and negative excess charges, as represented by the two vesicle phases in Fig. 2a. Comparing the two vesicle phases on opposite sides of the equimolar line in the tetracaine system, one can see that the vesicles are larger in the tetracaine-rich area (Fig. 3B). It also seems that the size of the vesicles is dependent on the concentration ratio between the drug and surfactant and not on the total concentration. Diphenhydramine, however, seems unable to form vesicles in the drug-rich region, as only one vesicle phase is seen.

Table II. Diffusion Coefficients with Standard Deviations (n = 3)

Formulation	D (cm^2/s)	SD
Diphenhydramine 14 mM, C940 1%*	$6.09 \cdot 10^{-6}$	$\pm 5.4 \cdot 10^{-7}$
Diphenhydramine 14 mM, SDS 26 mM, C940 1%*	$4.11 \cdot 10^{-7}$	$\pm 6.5 \cdot 10^{-8}$
Diphenhydramine 7 mM, C940 1%*	$6.94 \cdot 10^{-6}$	$\pm 9.4 \cdot 10^{-7}$
Diphenhydramine 7 mM, SDS 13 mM, C940 1%*	$6.64 \cdot 10^{-7}$	$\pm 1.8 \cdot 10^{-7}$
Diphenhydramine 8 mM, SDS 32 mM, C940 1%*	$4.75 \cdot 10^{-7}$	$\pm 2.7 \cdot 10^{-7}$
Tetracaine 14 mM, C940 1%*	$3.65 \cdot 10^{-6}$	$\pm 3.8 \cdot 10^{-7}$
Tetracaine 14 mM, SDS 26 mM, C940 1%	$6.04 \cdot 10^{-8}$	$\pm 4.3 \cdot 10^{-9}$
Tetracaine 14 mM, agar 0.1%	$8.41 \cdot 10^{-6}$	$\pm 1.8 \cdot 10^{-7}$
Tetracaine 14 mM, SDS 26 mM, Agar 0.1%	$3.19 \cdot 10^{-8}$	$\pm 1.9 \cdot 10^{-8}$
Tetracaine 26 mM, agar 0.1%	$9.08 \cdot 10^{-6}$	$\pm 1.5 \cdot 10^{-7}$
Tetracaine 26 mM, SDS 14 mM, Agar 0.1%	$1.89 \cdot 10^{-6}$	$\pm 2.5 \cdot 10^{-8}$
Diphenhydramine 14 mM, SDS 26 mM, C940 1%, pH = 11.7	$1.40 \cdot 10^{-6}$	$\pm 1.8 \cdot 10^{-7}$

* Gels prepared according to the alternative method, mixing solution with neutralized gel in the ratio 1:1.

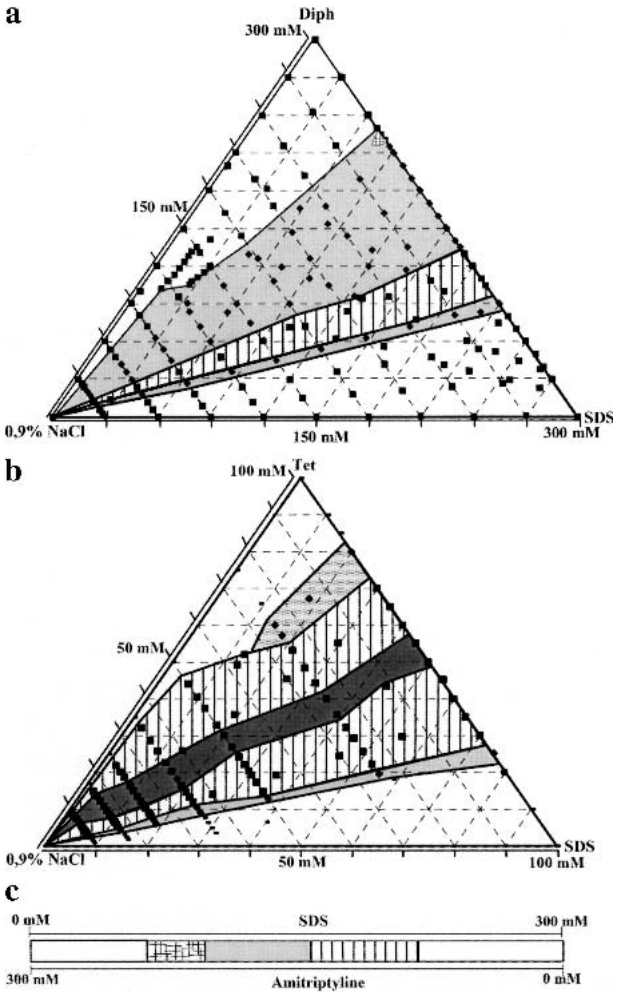

Fig. 2. Phase diagrams, where white areas represent micellar/aqueous solution, the gray areas represent two-phase regions, black areas represent precipitates, the cross-lined areas represent the bluish phase, and the striped areas represent the vesicle phase. a, Three-component phase system containing diphenhydramine, SDS, and 0.9% NaCl in water. b, Three-component phase system containing tetracaine, SDS, and 0.9% NaCl in water. c, Phase areas at a total concentration of 300 mM amitriptyline/SDS in 0.9% NaCl in water.

Micelles

In the diphenhydramine–SDS phase diagram in Fig. 2a, it is evident that the vesicle phase on the SDS-rich side was first followed by a two-phase region and then a visually clear micellar region as the concentration of SDS was increased. Samples of the micellar phase adjacent to the two-phase region contained elongated as well as branched micelles (Fig. 3c,d). As the concentration of SDS was increased without changing the total concentration of surfactant and drug, the micelles became less elongated and eventually spherical as the composition came closer to 100% SDS. In Fig. 4 the viscosity of samples with micelles, branched micelles and vesicles are shown as a function of sample composition. The SDS-rich samples had a viscosity resembling that of water, but as the composition got richer in diphenhydramine, the micelles became elongated, and the viscosity increased. The viscosity of the vesicle phase was also high because of the increase in vesicle size or the vesicle spheres coming in close contact with each other at these concentrations.

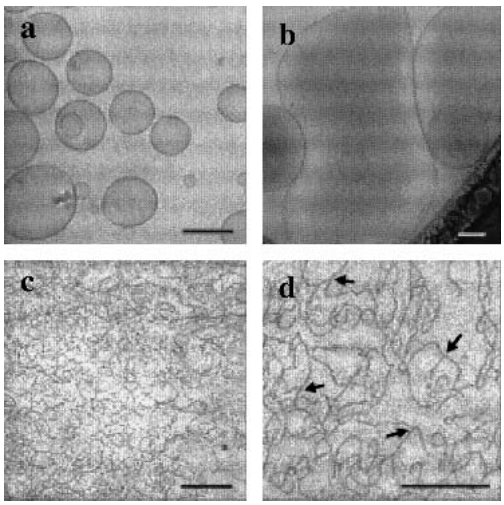

Fig. 3. Cryo-TEM pictures of catanionic mixtures in 0.9% NaCl: (a) 14 mM tetracaine/26 mM SDS; (b) 26 mM tetracaine/14 mM SDS; (c,d) 8 mM diphenhydramine/32 mM SDS. The bar indicates 200 nm.

On the drug-rich side of the phase diagrams of both tetracaine and diphenhydramine, micellar phases were found. The micelles appear to be spherical or to have only minor elongations, having little or no effect on the rheologic behavior of the samples.

Other Phases

In the diphenhydramine system a two-phase region coincided with the equimolar region in the phase diagram. A second two-phase region was also visible between the vesicle phase and the SDS-rich micellar phase. At the border between the vesicle and the two-phase region, foggy vesicle solutions were noticed. These, however, were not classified as two-phase solutions because there was no separation of phases even after a couple of weeks.

In contrast to the tetracaine system, no obvious second vesicle phase was discovered for the diphenhydramine system in the concentration range studied. There is, however, still

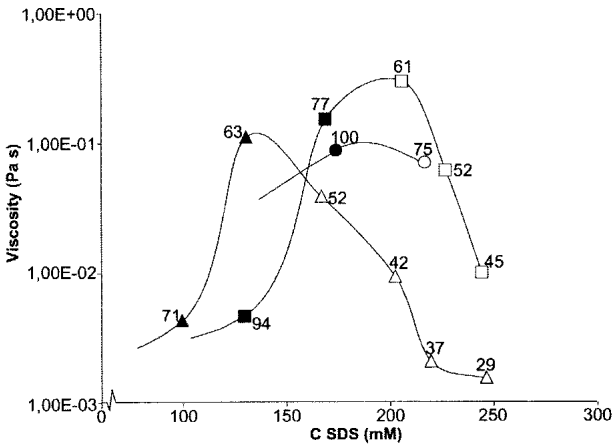

Fig. 4. Viscosity at a shear rate of 11.6 s^{-1} on mixtures containing diphenhydramine, SDS, and water—single samples. The concentration of diphenhydramine is specified at some selected points, where filled symbols represent the vesicle phase and open symbols represent micellar/aqueous solution.

one interesting area to explore on the drug-rich side for diphenhydramine. Where the total concentration of diphenhydramine and SDS reaches 300 mM, there is an area of clear, vaguely blue-colored solution surrounded by the two-phase regions. These bluish phases have been found in other systems previously (5).

The tetracaine system exhibited a phase behavior quite similar to that of diphenhydramine. However, two major differences render it a more complex system. As in the diphenhydramine system, micelles, two-phase areas, and vesicles were found. In addition to this, a phase of solid precipitates was discovered, close to equimolarity. The most interesting difference, however, is the second vesicle phase on the tetracaine-rich side, which is discussed above.

Amitriptyline showed a phase behavior that was close to that of diphenhydramine, and therefore detailed data are not presented for this compound.

Salt and pH Dependence

Because the samples studied in this report were all prepared in 0.9% NaCl solutions, further addition of small amounts of NaCl should not affect the samples. This was confirmed for the vesicle phase (composition 14 mM diphenhydramine and 26 mM SDS), which did not appear to have been affected when examined with the naked eye, when small amounts of salt had been added. However, at 3.6% NaCl, the vesicle phase started to turn somewhat "foggy," and at 5.4% NaCl the "fog" was even more apparent. The addition of salt influences the electrostatic interactions of the polar groups of the amphiphiles and can induce, e.g., the vesicle-to-micelle transition. In a study by Sein and Engberts (21), alkali metal chloride salts were seen to transform micelles of double-tailed amphiphiles to vesicles. Salt can induce micellar growth from spherical micelles to produce elongated and branched micelles (23), an effect that has been seen using rheology for catanionic drug–surfactant mixtures (13).

In the limited pH study performed, the vesicles studied (with composition of 14 mM diphenhydramine and 26 mM SDS) were stable and did not exhibit any notable effects in the region with pH 0.5–10. When the pH is raised 1 unit above the pK_a of diphenhydramine, the vesicle phase became clear, and micelles were formed instead of vesicles. However, when the pH is lowered below the pK_a of SDS, phase separation did not occur until 6 weeks had passed. A change of pH has previously been seen to change vesiculation and vesicle stability (22).

Further studies are in progress on both pH and salt dependence.

Temperature Dependence

The zero-shear viscosity, determined from the Newtonian region at low shear rates, of a sample of the vesicle phase (with composition of 120 mM diphenhydramine and 180 mM SDS) was not affected (determined to about 0.3–0.5 Pa·s) when the temperature was varied between 5 and 40°C. Florence *et al.* also reported that the relative viscosity of vesicles changed only little with increasing temperature (23). However, the viscosity, η, of the branched micellar phase (composition 60 mM diphenhydramine, 240 mM SDS) decreased substantially as the temperature was increased from 5 to 60°C. At the lowest temperature the viscosity was 5 Pa·s; at 37°C the viscosity was 0.2 Pa·s; and at higher temperatures, the viscosity of water (1 mPa·s) was reached. It has previously been reported that elongated micelles of charged surfactants will decrease in size and become more spherical on heating, causing a decrease in the viscosity (23).

Drug Release Measurements

For the initial period of time, used for calculation of diffusion coefficients, the release is diffusion controlled; i.e., n [Eq. (1)] is 0.5. As time increases, though, the kinetics for vesicle and micelle formulations will partly cease being diffusion controlled, resulting in a change of the n value. This is not surprising because there will probably be phase transitions in the gels as free drug compound or free SDS will move more rapidly through the gels than any compound bound in the vesicles or micelles, making the compositions change by time.

The release of diphenhydramine from C940 gels can be seen in Fig. 5. Even though some formulations appear to release more than 100%, as discussed above, the light-scattering effect of the polymer is probably equal from all formulations, which would make valid comparison between formulations possible. The vesicles in C940 (Fig, 6) were more multilamellar and appeared to be larger than those seen in polymer-free samples. Phases with branched micelles also seemed to have a more complex network. The drug release from the formulation with 14 mM drug and 26 mM SDS was significantly slower than that from the surfactant-free reference gel ($p < 0.001$). A cryo-TEM picture of this formulation (Fig. 6a) revealed that vesicles were present in the gel. Furthermore, the formulation with 8 mM diphenhydramine and 32 mM SDS was significantly slower than the reference sample ($p < 0.001$). Cryo-TEM showed that branched micelles were formed in the gel (Fig. 6b). The diphenhydramine diffusion coefficient was about 10 times lower when the drug was allowed to form vesicles or branched micelles with SDS compared to the release from gels containing only the drug compound. The release rate did not differ between micellar and vesicular formulations (see Fig. 5 and Table II).

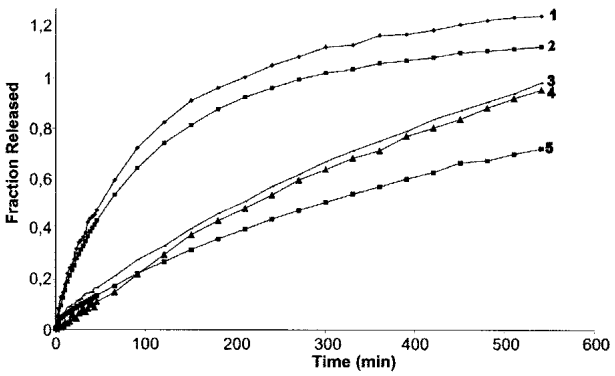

Fig. 5. The release of diphenhydramine from different formulations. (1) Diphenhydramine 7 mM, C940 1%. (2) Diphenhydramine 14 mM, C940 1%. (3) Diphenhydramine 7 mM, SDS 13 mM, C940 1%. (4) Diphenhydramine 8 mM, SDS 32 mM, C940 1%. (5) Diphenhydramine 14 mM, SDS 26 mM, C940 1%. The fraction released sometimes appears to exceed 100% because of light-scattering effects from the polymer.

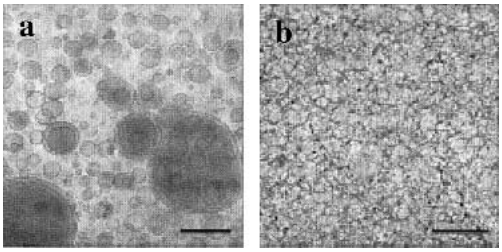

Fig. 6. Cryo-TEM pictures of catanionic mixtures in 1% C940: (a) 14 mM diphenhydramine/26 mM SDS; (b) 8 mM diphenhydramine/32 mM SDS. The bar indicates 200 nm.

In Fig. 7 the release of tetracaine from C940 and agar can be seen. Although tetracaine is oppositely charged with regard to the polymer, and electrostatic drug–polymer interactions could be anticipated, the release rate was not different from the anionic C940 than from the uncharged agar gels. When the concentration of drug was 26 mM or higher, the positive charges of the drug will shield and neutralize the carboxylic groups of the polymer, impeding the swelling of the hydrogel. No homogeneous gels were formed at this high tetracaine concentration, and in order to evaluate the release from phases with high drug concentrations, uncharged agar gels must be used. The interactions between the gel matrix and surfactant aggregates can improve the sustained release from gels, but it is not essential because the slow diffusion of drug trapped in surfactant aggregates is the major cause of the slower release rate (20). In this study only small differences in the rheologic behavior of the gel formulations was seen, indicating that the mucosal residence time of the gels is not affected. The small differences observed probably derived from interactions between the drug and the polymer (24) and the salt sensitivity of Carbopols (25), as an increased concentration of drug compound also results in an increased concentration of counterions.

When mixed with SDS (14 mM or 26 mM), tetracaine formed vesicles on both the surfactant-rich and the drug-rich side of the phase diagram. The two different tetracaine vesicles (14 mM tet./26 mM SDS and 26 mM tet./14 mM SDS) had different degrees of sustained release ($p < 0.001$): tetracaine from the drug-rich vesicle phase was released faster (see also diffusion coefficients in Table II). This was probably a result of different degrees of unbound tetracaine in the systems because the vesicles are often formed at an equimolar surfactant ratio (26), causing the vesicle phase on the tetracaine-rich side to contain an excess of unbound tetracaine and the vesicle phase on the SDS-rich side to contain an excess of unbound SDS. Another possibility is that the tetracaine-rich vesicles might be less stable, and therefore, there would be a larger amount of free tetracaine to be released.

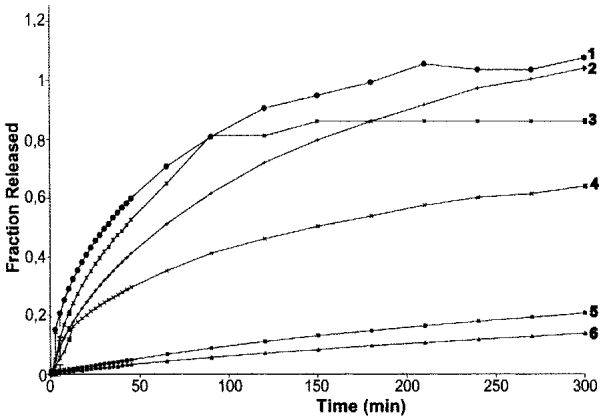

Fig. 7. The release of tetracaine from different formulations. (1) Tetracaine 14 mM, agar 0.1%. (2) Tetracaine 14 mM, C940 1%. (3) Tetracaine 26 mM, agar 0.1%. (4) Tetracaine 26 mM, SDS 14 mM, agar 0.1%. (5) Tetracaine 14 mM, SDS 26 mM, C940 1%. (6) Tetracaine 14 mM, SDS 26 mM, agar 0.1%. The fraction released sometimes appears to exceed 100% because of light-scattering effects from the polymer.

The release of the pH 11.7 gel was slower than the SDS-free reference ($p < 0.001$) but faster than release from a gel at pH 7.4 ($p < 0.05$). This could be explained by there being no vesicles present at a pH above the pK_a of diphenhydramine, but the release of diphenhydramine is still affected by electrostatic interactions with SDS micelles or by being partly solubilized in the SDS micelles.

Applications

SDS has, however, toxic properties when in contact with mucosa (27). Because of this, the drug-rich vesicle region of tetracaine is the pharmaceutically more interesting one. A higher drug load is preferable as well, minimizing excipients in the formulation. Still, there are other applications where the potential toxicity of SDS-rich vesicles needs not to be considered, e.g., cutaneous formulations.

CONCLUSIONS

Phase diagrams of the three different cationic drug compounds diphenhydramine, tetracaine, and amitriptyline mixed with the anionic surfactant SDS showed that although the diagrams may differ in some parts, vesicles and branched micelles were present in all three diagrams.

With use of vesicles and micelles formed from catanionic systems in gels, sustained release may be accomplished. The effect is equally pronounced when either of the two phases is used. In that way, the long mucosal contact time of the gel can be fully used, probably resulting in a greater bioavailability. However, the potential toxicity of SDS needs to be considered, depending on the route of administration. Further studies on polymers used together with catanionic mixtures will give a better understanding of how to fully obtain a controlled release *in vitro*.

ACKNOWLEDGMENTS

Göran Karlsson is greatfully acknowledged for extraordinarily good work with the cryo-TEM. We wish to thank Anna Imberg for supporting us with the Excel template for our phase diagrams and Göran Svensk for helping us with the drop-weight technique. Annika Ridell and Andreas Hugerth have made valuable contributions too regarding CMC measurements.

REFERENCES

1. H. Fukuda, K. Kawata, and H. Okuda. Bilayer-forming ion-pair amphiphiles from single-chain surfactants. *J. Am. Chem. Soc.* **112**: 1635–1637 (1990).

2. P. Jokela, B. Jönsson, and A. Kahn. Equilibria of catanionic surfactant–water systems. *J. Phys. Chem.* **91**:3291–3298 (1987).
3. E. W. Kaler, A. K. Murthy, B. E. Rodriguez, and J. A. Zasadzinski. Spontaneous vesicle formation in aqueous mixtures of single-tailed surfactants. *Science* **245**:1371–1374 (1989).
4. C. Tondre and C. Caillet. Properties of the amphiphilic films in mixed cationic/anionic vesicles: a comprehensive view from a literature analysis. *Adv. Colloid Interface Sci.* **93**:115–134 (2001).
5. E. F. Marques, O. Regev, A. Khan, M. G. Miguel, and B. Lindman. Vesicle formation and general phase behaviour in the catanionic mixture SDS-DDAB-water. The anionic-rich side. *J. Phys. Chem. B.* **102**:6746–6758 (1998).
6. E. F. Marques. Size and stability of catanionic vesicles: Effects of formation path, sonication, and aging. *Langmuir* **16**:4798–4807 (2000).
7. L. L. Brasher and E. W. Kaler. A small-angle neutron scattering (SANS) contrast variation investigation of aggregate composition in catanionic surfactant mixtures. *Langmuir* **12**:6270–6276 (1996).
8. J. M. Corkill, J. F. Goodman, S. P. Harrold, and J. R. Tate. Monolayers formed by mixtures of anionic and cationic surface-active agents. *Trans. Faraday Soc.* **63**:247–256 (1996).
9. L. E. Bromberg. Enhanced nasal retention of hydrophobically modified polyelectrolytes. *J. Pharm. Pharmacol.* **53**:109–114 (2001).
10. J. Carlfors, K. Edsman, R. Petersson, and K. Jörnving. Rheological evaluation of Gelrite *in situ* gels for ophthalmic use. *Eur. J. Pharm. Sci.* **6**:113–119 (1998).
11. G. M. Grass and J. R. Robinson. Relationship of chemical structure to corneal penetration and influence of low viscosity solution on ocular bioavailability. *J. Pharm. Sci.* **73**:1021–1027 (1984).
12. N. A. Peppas, P. Bures, W. Leobandung, and H. Ichikawa. Hydrogels in pharmaceutical formulations. *Eur. J. Pharm. Biopharm.* **50**:27–46 (2000).
13. M. Paulsson and K. Edsman. Controlled drug release from gels using surfactant aggregates: II. Vesicles formed from mixtures of amphiphilic drugs and oppositely charged surfactants. *Pharm. Res.* **18**:1586–1592 (2001).
14. R. M. Minardi, P. C. Schultz, and B. Vuano. Triangular phase diagram of the catanionic system dodecyltrimethylammonium bromide-disodium dodecanephosphonate-water. *Colloids Surf. A.* **197**:167–172 (2002).
15. C. M. Wilkinson. Extended use of, and comments on, the drop-weight (drop-volume) technique for the determination of surface and interfacial tensions. *J. Colloid Interface Sci.* **40**:14–26 (1972).
16. M. Almgren, K. Edwards, and G. Karlsson. Cryo transmission electron microscopy of liposomes and related structures. *Colloid Surf. A-Physicochem. Eng. Asp.* **174**:3–21 (2000).
17. L. Bohlin. New instrumentation for advanced rheometry. *Suppl. Rheol. Acta.* **26**:161–164 (1988).
18. W. I. Higuchi. Analysis of data on the medicament release from ointments. *J. Pharm. Sci.* **51**:802–804 (1962).
19. P. L. Ritger and N. A. Peppas. A simple equation for description of solute release I. Fickian and non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. *J. Control. Release* **5**:23–26 (1987).
20. M. Paulsson and K. Edsman. Controlled drug release from gels using surfactant aggregates: I. Effect of lipophilic interactions for a series of uncharged substances. *J. Pharm. Sci.* **90**:1216–1225 (2001).
21. A. Sein and J. B. F. N. Engberts. Micelle to lamellar aggregate transition of an anionic surfactant in dilute aqueous solution induced by alkali metal chloride and tetraalkylammonium chloride salts. *Langmuir* **11**:455–465 (1995).
22. H. Hauser, N. Gains, and M. Muller. Vesiculation of unsonicated phospholipid dispersions containing phosphatidic acid by pH adjustment: Physicochemical properties of the resulting unilamellar vesicles. *Biochemistry* **22**:4775–4781 (1983).
23. A. T. Florence, P. Arunothayanun, S. Kiri, M. S. Bernard, and I. F. Uchegbu. Some rheological properties of nonionic surfactant vesicles and the determination of surface hydration. *J. Phys. Chem. B* **103**:1995–2000 (1999).
24. M. Paulsson and K. Edsman. Controlled drug release from gels using lipophilic interactions of charged substances with surfactants and polymers. *J. Colloid Interface Sci.* **248**:194–200 (2002).
25. N. W. Taylor and E. B. Bagley. Dispersions or solutions? A mechanism for certain thickening agents. *J. Appl. Polym. Sci.* **18**:2747–2761 (1974).
26. C. Caillet, M. Hebrant, and C. Tondre, Sodium octyl sulfate/cetyltrimethylammonium bromide catanionic vesicles: Aggregate composition and probe encapsulation. *Langmuir* **2000**:9099–9102 (2000)
27. K. Östh, M. Paulsson, E. Björk, and K. Edsman. Evaluation of controlled drug release and absorption from gels on pig nasal mucosa in a horizontal Ussing chamber. *J. Control. Release* **83**: 377–388 (2002).