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Review Article

Pharmaceutical applications for catanionic mixtures

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Abstract

Mixtures of oppositely charged surfactants, so called catanionic mixtures, are a growing area of research. These mixtures have been shown to form several different types of surfactant aggregates, such as micelles of various forms and sizes, and lamellar structures, such as vesicles. In this review, a short introduction to the field of catanionic mixtures is presented and the pharmaceutical possibilities offered by such mixtures are reviewed. There are several interesting ideas on how to apply catanionic mixtures to improve the delivery of, for example, drug compounds and DNA, or for HIV treatment.

Introduction

The term "catanionic mixtures" is a relatively new one in the field of colloidal science, but in recent years, mixtures of two oppositely charged surfactants, so called catanionic mixtures or catanionic surfactants, have attracted increasing attention. Mixtures of surfactants have been studied extensively over the years and there is also a small number of older studies on mixtures of oppositely charged surfactants (Anacker 1953; Collison & Lawrence 1959; Hayer et al 1961; Barker et al 1974; Hargreaves & Deamer 1978), but the term catanionic mixtures was not applied to these until Jokela et al first used it in 1987. Jokela et al (1987) studied four different equimolar mixtures of oppositely charged surfactants and reported swollen lamellar phases in all of them. A couple of years later, Kaler et al (1989) published a study on spontaneous vesicle formation in aqueous mixtures of positively charged cetyltrimethylammonium tosylate (CTAT) and negatively charged sodium dodecylbenzene sulfonate (SDBS), and since then the number of articles published on catanionic mixtures has increased every year. Figure 1 illustrates the developing interest in this area by listing the number of hits when searching on the term "catanionic" in the Chemical Abstracts Plus database (Chemical Abstracts Service, OH, USA). Clearly, the number of articles per year has increased annually, signifying a juvenile area on its way up. The terminology has also evolved during the years, and today there are not only one but two terms describing mixtures of oppositely charged surfactants: catanionic mixtures (or surfactants) and ion-pair amphiphiles (IPAs); the latter term, to the best of our knowledge, was first used by Fukuda et al (1990). In the earlier years there was some confusion about what the two different terms signified but nowadays it is generally agreed that the distinction between the two terms is that the counterions of the two surfactants have been removed in IPAs, whereas the counterions coexist in a catanionic mixture (Tondre & Caillet 2001). In this paper we review the potential pharmaceutical applications of catanionic mixtures. The review is restricted to water-soluble systems and we focus on non-phase-separated systems in the low concentration regions. In addition, ion-pair amphiphiles will be discussed, although naturally it is a problem to keep a system salt-free in a physiological environment. The majority of studies on catanionic systems address the physicochemical aspects of the systems, however more recently several potential applications have been suggested. These applications will be described later in this review, but first we will give a brief introduction to some interesting features of catanionic mixtures.

What is a catanionic mixture?

A classical example of the symmetric phase diagram of a diluted catanionic system is illustrated in Figure 2, in which is displayed a micelle phase and a vesicle phase surrounded by a multiphase region, on each side of the phase diagram, separated by

Abbreviations[a]

ALA	Arginine-N-lauroyl amide hydrochloride
CF	Carboxyfluorescein
CTAB	Cetyltrimethylammonium bromide
C8TAB	Octyltrimethylammonium bromide
CTAOH	Cetyltrimethylammonium Hydroxide
CTAT	Cetyltrimethylammonium tosylate
DDAB	Didodecyl dimethylammonium bromide
DDACl	Dodecylammonium chloride
DeACl	Decylammonium chloride
DTAB	Dodecyl trimethylammonium bromide
DoTAC	Dodecyl trimethylammonium chloride
DPPC	1,2 dipalmitoy1-sn-glycero-3-phosphatidylcholine
DSDP	Disodium dodecanephosphonate
DTAB	Dodecyltrimethylammonium bromide
DVB	Dvinylbenzene
FITC	Fluorescein isothiocyanate
HEC	Hydroxyl ethyl cellulose
HS	Sodium hydrogenated tallow glutamate
HTMAB	Hexadecyltrimethylammonium bromide
IPA	Ion pair amphiphile
LAM	N?-lauroyl-arginine-methyl ester hydrochloride
MIPA	Multiple chain ion pair amphiphile
MUBS	4-(?-methacrylyoloxyundecyl) oxy benzene sulfonate
MUTB	Methacryloyloxyundecyl trimethylammonium bromide
NaOA	Sodium oleate
SCS	Sodium cetyl sulfte
SD	Sodium dodecanoate
SDBS	Sodium dodecyl benzene sulfonate
SDeS	Sodium decyl sulfate
SDS	Sodium dodecyl sulfonate
SOS	Sodium octyl sulfate
STDA	Sodium tetradecyl sulfate
TDAC1	Tetradecylammonium chloride
TTAB	Tetradecyltrimetylammonium bromide
V+	Vesicle rich in the cationic surfactant
V-	Vesicle rich in the anionic surfactant

[a]These abbreviations are the same as those used in the original articles.

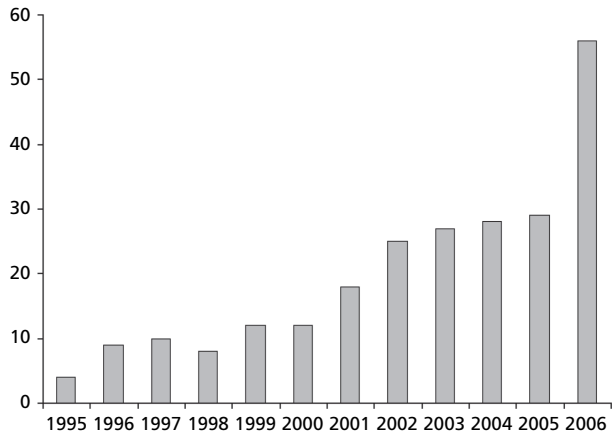


Figure 1 The number of hits for the term "catanionic" in the Chemical Abstracts Plus database, illustrated as hits per year.

precipitation. The figure resembles the phase diagram of CTAT/SDBS published by Kaler et al (1989) and similar catanionic phase behaviour has been reported in other systems,

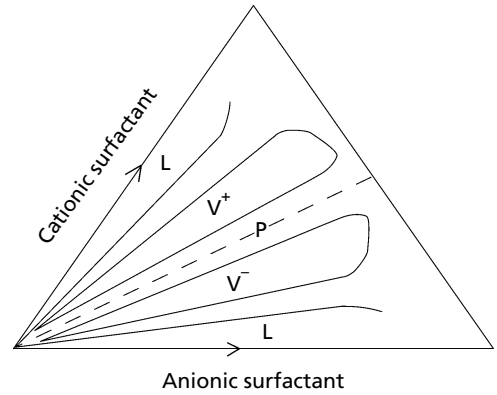


Figure 2 Schematic of a classical phase diagram for a catanionic mixture, where L represents micellar/aqueous solution, V^+ represents positively charged vesicles, V^- represents negatively charged vesicles, and P represents precipitate.

for example DoTAC/SD (Regev & Khan 1996), SDS/DDAB (Marques et al 1998, 1999b) and SDS/tetracaine (Bramer et al 2003). However, there are numerous variations in the appearance of the catanionic phase diagram. Gradzielski (2003) notes how the chain lengths of the two different surfactants in a catanionic system affect the symmetry of the phase diagram: the larger the difference in chain length, the more the asymmetry in the phase diagram. The types of structures that are formed mainly depend on the cationic/anionic ratio, but also on the total concentration at a certain ratio.

The different types of structures that can be found in catanionic mixtures are more thoroughly described in a recent review by Hao & Hoffmann (2004); in the present review we concentrate on catanionic micelles and catanionic vesicles.

Catanionic micelles

It is common for ionic surfactants to form spherical micelles when dissolved in water, a process driven by the gain in free energy caused by a reduction in the contact area between water and hydrocarbons (Tanford 1991). However, when one surfactant is mixed with another surfactant, not only can various other structures form, but the micelles themselves often adopt new forms. Micelles of various sizes and shapes are generally found in catanionic mixtures, including globular, elongated (worm-like) and branched ones. The micelle size in a catanionic system depends on both the ratio of the two surfactants and on the total concentration at a certain ratio.

Schulz et al (1999) used the surface tension, conductivity and solubilization of the hydrophobic agent Sudan III as indirect measurements of micellar formation and growth in the DTAB/DSDP system. By increasing the total concentration of DTAB/DSDP at a certain ratio, the aggregates went from ion-pairs to micelles at the mixed critical micelle concentration, which then grew to form large rod-like micelles when the concentration was further increased. In

addition, it has been reported that the micellar size in catanionic systems increases the closer to equimolar the cationic/anionic ratio is within the micellar regions of a phase diagram (Bergstrom & Pedersen 1998, 1999; Bramer et al 2003). For instance, by means of rheological characterization Bramer et al (2003) showed how the viscosity of catanionic diphenhydramine/SDS mixtures increased as the compositions were closer to the equimolar ratio because of the increased micellar size. Contrary to this, however, in a study by Marques et al (2000), it was shown that neither the molar ratio nor the total surfactant ratio affected the size of STDC/DDAB micelles when studied by nuclear magnetic resonance self-diffusion and cryo-transmission electron microscopy.

The dependence of the symmetry of the surfactant tail lengths on micellar size was investigated in mixtures of NaOA/C_nTAB (Raghavan et al 2002a). It was concluded that for one long and one very short tail length, the micellar growth was weak. For tails of equal lengths, the interactions were of such strength that bilayer structures were formed in a wide range of compositions. The largest micellar growth occurred in a mixture of two surfactants, one having a long tail and the other with a moderately long tail. In a study by Filipovic-Vincekovic et al (1995), three different catanionic mixtures were investigated, DeACl/SDeS, DDACl/SDS and TDACl/STDS with 10, 12 and 14 carbon atoms in the chain, respectively. It was reported that an increase in the alkyl chain lengths of the anionic and the cationic surfactant increased the tendency for micellization to occur, but that the increased chain lengths also increased the tendency to precipitate.

Catanionic vesicles

Traditionally, several different methods are used for the preparation of vesicles, such as sonication, thin-film hydration or high-pressure extrusion, whereas for other situations it may be sufficient to vortex or just shake a mixture vigorously to accomplish vesicle formation (Gradzielski 2003). Thus, one of the particularly interesting features of catanionic vesicles is their ability to form spontaneously. This was first noted by Kaler et al (1989), who reported spontaneous vesicle formation in three different catanionic systems, and since this initial publication this has been supported by many other authors for numerous systems (Ambuehl et al 1993; Herrington et al 1993; Kondo et al 1995; Regev & Khan 1996; Marques et al 1998, 1999b; Salkar et al 1998; Marques 2000; Bergstrom 2001; Jung et al 2001; Tondre & Caillet 2001; Shioi & Hatton 2002; Bramer et al 2003; Gradzielski 2003). However, as spontaneous formation means that no shear forces whatsoever are necessary for vesicle formation, it is difficult to prove, since it is almost impossible to mix something without the sample being exposed to some kind of shear force.

The idea of the vesicle as a thermodynamically equilibrated state has been discussed more thoroughly than the spontaneous formation. For example, Laughlin (1997) has dedicated an article entirely to this subject, in which he states that from a thermodynamic point of view, vesicles are not to be considered to be in an equilibrium state. Almgren & Rangelov (2004) and Marques (2000) have, independently of each other, conducted similar studies in which the influence of the mixing procedure on catanionic systems was investigated. Both studies showed that there was an influence from the mixing procedure but the interpretation of the results differed, with Marques claiming that the results were in favour of the vesicle as an equilibrium state and Almgren and Rangelov claiming the opposite.

However interesting the discussions on spontaneous formation and the thermodynamic equilibrium may be, it is of limited value for most potential applications. Clearly, vesicles are readily formed in numerous catanionic systems and they appear to possess long-term stability qualities.

There is vast variation in size and polydispersity for the catanionic vesicles within each system, depending on the cationic/anionic molar ratio, as well as between different systems. Typical catanionic vesicles, as far as one can talk of such things, span a size of a couple of hundred nanometres. However, vesicles as small as 20 nm are commonly found (Kaler et al 1992; Marques et al 1998, 1999b; Jung et al 2001; Bramer et al 2003; Coldren et al 2003; Segota et al 2005), as are vesicles with a diameter of at least several micrometres (Villeneuve et al 1999; Hao et al 2000; Marques 2000; Segota et al 2005; Bramer et al 2006). There is also a variation in the lamellarity of the catanionic vesicles, with both unilamellar vesicles and multilamellar vesicles being encountered frequently in the catanionic systems.

Some other catanionic structures

The structural variation in different catanionic systems is pronounced. Not only are mixed micelles and vesicles common, but several other more complex structures have been reported. For example, hollow polyhedrons have been found in catanionic mixtures of myrstic acid and CTAOH (Dubois et al 2001; Lootens et al 2003; Delorme et al 2006), as have catanionic discs (Zemb et al 1999). Other examples include Rosa et al (2006) who reported spontaneously formed cubosomes and hexosomes in catanionic mixtures of sodium hydrogenated tallow glutamate and arginine-*N*-lauroyl amide, and Blanzat et al (2001) who found helices and tubules in catanionic mixtures of 12-(4-amino-coumarin)-dodecanoic acid and *N*-octylaminolacticol.

Physiological prerequisites

When considering the eventual pharmaceutical applications of catanionic mixtures, the physiological prerequisites must be fully appreciated. A physiological environment usually means a neutral pH and an osmolality corresponding to 0.9% NaCl. In most cases, it can be expected that a catanionic mixture will be affected by both the pH and the ionic strength of its immediate environment. In addition, it is necessary to work within a limited temperature window, although it has been shown in a study by Backlund et al (1997) that temperature plays a minor role only on the phase extensions in an octylamine/octanoic acid catanionic system. Similarly, in catanionic mixtures of alkyltriethylammonium bromide and sodium alkylsulfonate, it was concluded that the temperature had only a limited impact on the polydispersity and the radius of the aggregates formed (Chen et al 2002).

It is has long been known that salts alter the critical micelle concentration of various surfactants (Wan & Poon 1969). Furthermore, the size and shape of the micelles formed can be affected by the salt screening the repulsion between charged headgroups (Mazer et al 1976; Hoffmann et al 1982; Khatory et al 1993; Hassan et al 2002; Raghavan et al 2002b). Moreover, the addition of salt has an impact on catanionic aggregates, for example Brasher et al (1995) showed how an increased amount of sodium bromide caused a micelle to vesicle phase shift in a mixture of CTAB and SOS.

Obviously the physiological environment will differ depending on the administration route selected, which calls for extensive knowledge on how a catanionic mixture will react to the intended environment. For example, there are, to the best of our knowledge, no administration routes where the formulation is not in contact with salts, which probably makes IPAs less suitable than regular catanionic mixtures for pharmaceutical applications. Similar consideration needs to be given to any potential catanionic pharmaceutical formulation. Also, the behaviour of one-component systems for the cation and anion should be studied in a physiological environment for a more complete understanding of a potential pharmaceutical application.

Applications

Several of the applications for catanionic complexes are the same as for other surfactant complexes, for example the catanionic micelles could be used for the same purposes as single surfactant micelles and the catanionic vesicles may be used as an alternative to liposomes. There are also examples of applications where the specific properties of catanionic complexes can be used. Some of the different applications suggested are described below. Some possible applications where only single studies have been made, such as the use of catanionic surfactant mixtures for wall coatings in capillary electrophoreses (Wang & Lucy 2004) and for solubilization of fullerenes (Li et al 2006), have not been included.

Encapsulation of drugs into catanionic vesicles

The use of catanionic vesicles as carrier systems has been studied using model compounds such as glucose, sucrose, carboxyfluorescein (CF) and riboflavin. The main issues have been the encapsulation efficiency, permeability and stability of the vesicles. The studies made before 2001 are summarized by Tondre & Caillet (2001). In the studies reviewed by Tondre & Caillet (2001), the encapsulation efficiency varied up to a maximum of 7.9% and was dependent on the catanionic system used. It was shown that the molar ratio of the cationic and anionic surfactant affects the encapsulation in the DDAB/SDS system (Kondo et al 1995). The permeability and stability of the vesicles have been shown to vary with temperature (Hargreaves & Deamer 1978) and the release rate of the encapsulated probe has been shown to be dependent on the presence of electrolytes (Chung & Lee 1999; Chung et al 2000). When studying the encapsulation efficiency of IPA vesicles (CTA^+/palmitic acid), it was found that the IPA vesicle bilayer was more loosely packed than the one made from DPPC (Chung et al 1992). The use of multichain amphiphiles to improve the membrane tightness was also reported (Bhattacharya et al 1998; Chung et al 1998). Tondre & Caillet (2001) concluded that the results at that time seemed to indicate that the vesicles were extremely leaky and that the encapsulation by IPA is not as effective as the encapsulation performed by phospholipids.

However, since then several attempts have been made to understand and increase the membrane stability and the encapsulation efficiency of the catanionic systems. The systems chosen for investigation have been traditional single-chain catanionic vesicles as well as multichain and polymerized vesicles.

Single-chain surfactant systems The traditional and most common catanionic/IPA systems studied are the ones consisting of two oppositely charged amphiphiles, each with one single alkyl chain. Caillet et al (2000) studied the encapsulation of CF, riboflavine and glucose in CTAB/SOS vesicles as well as in the corresponding IPA vesicles (CTA^+/OS^-). The encapsulation of CF was extremely low (<0.01%), which was attributed to the ionic character of the probe, which might destabilize the vesicles. A better entrapment capacity, but still only about 1%, was found using glucose. The entrapment capacity was better in the IPA vesicles where all counter ions had been removed, provided that the IPA system was allowed to age for 24 h. The release of glucose was rapid, complete and independent of the presence or absence of a membrane disrupting agent (in this case Triton X-100) indicating that the amphiphilic membrane has a very dynamic and permeable nature. It was suggested that the high permeability of the amphiphilic film depends on the short alkyl chain of the surfactants used since Kaler et al (1989) had already found that glucose could be efficiently encapsulated in CTAT/SDBS vesicles which remained stable for at least 1 year.

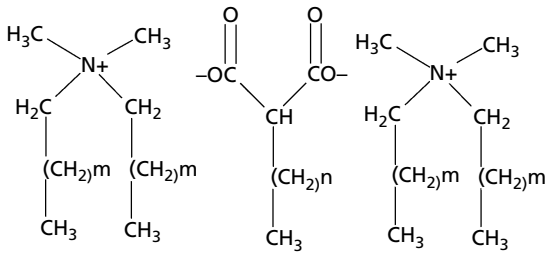
The system CTAT/SDBS was further investigated in a subsequent study by Fischer et al (2002) in which three vesicle compositions were used, V^+ (with an excess of CTAT), V^- (with an excess of SDBS) and pure IPA vesicles without counter ions present. The CTAT-rich vesicles were the least efficient at entrapping glucose, whereas the SDBS-rich and the IPA vesicles were approximately equivalent. The intrinsic encapsulated volume, even at very low surfactant concentrations, was greatest for the IPA vesicles, but in the long term, the IPA vesicles seemed to be less stable than the V^- vesicles. In the glucose release studies it was shown that the amphiphilic bilayer was very permeable, though less permeable than in the CTAB/SOS system studied earlier (Caillet et al 2000).

In a recent study by Wang et al (2006), the encapsulation efficiency and the permeability of CF were studied in both positively and negatively charged CTAT/SDBS vesicles and compared with phospholipid vesicles formed from egg yolk phosphatidylcholine (EYPC). The SDBS-rich vesicles gave highly irreproducible results, the encapsulation into CTAT-rich vesicles was 21%, while the EYPC vesicles only encapsulated 1.6%. The reason for the large difference was that there is a specific interaction between the V^+ vesicles and CF that resulted in an electrostatic adsorption of CF (16%) to the charged bilayer, but only a small amount was adsorbed to the EYPS vesicles (0.4%). The permeability of the catanionic membrane was an order of magnitude lower than for the EYPC vesicles, with a very slow release of the

CF from the V^+ vesicles in comparison with that from the EYPC vesicles.

Multichain amphiphiles There are several studies where vesicles have been formed from ion pairs consisting of multichain amphiphiles. For some of the multichain amphiphiles, ion pair formation is not a prerequisite for vesicle formation since they can form vesicles themselves. In this section we only present results where the multichain amphiphiles have been used with an oppositely charged surfactant.

In an attempt to improve the membrane tightness, Chung et al (1998) have been using multiple-chain ion pair amphiphiles (MIPA); the amphiphiles are shown in Figure 3. The encapsulation of CF and the stability of the vesicles depended on the length of the alkyl chains; MIPA14 and MIPA18 showed good encapsulation and stability during dialysis, but this was not the case for MIPA16. The release of the encapsulated CF was almost zero but could be induced by the addition of surfactants (in this case SDS and Triton X-100), indicating good tightness of the amphiphile membrane. In a later study, Chung & Lee (1999) studied various combinations of the amphiphiles shown in Figure 4, concluding that the stability of the vesicles formed is highly dependent on the amphiphile components; the tightest membrane was obtained for an ion pair between amphiphiles B and C.



MIPA-14; n = 13, m = 12
MIPA-16; n = 15, m = 14
MIPA-18; n = 17, m = 16

Figure 3 Structure of the ion-pair amphiphiles used by Chung et al (1998).

Bhattacharaya et al (1998) studied the effects of the geometry of disubstituted aromatic units in bolaphile–amphiphile ion pairs. The bolaphiles, used together with two CTABs, are shown in Figure 5. The encapsulation of riboflavin and the permeation rate of hydroxide ions were studied. The permeability of the vesicle membrane was shown to depend on the geometry of the bolaphile; a *para*-substitution of the aromatic ring gave the tightest vesicle membrane.

IPA vesicles that are sensitive to changes in pH have also been under investigation using multichain amphiphiles, consisting of two positively charged ammonium surfactants together with a negatively charged dicarboxylate surfactant (see Figure 6) (Chung et al 2003a). The encapsulated CF was released quite slowly at a pH of 6, and faster at a pH of 9.5, but was dependent on the exact mixture of the surfactants used. The concept of pH-sensitive vesicles has been further investigated using polymerizable amphiphiles (Chung et al 2004a). These are further discussed below.

Polymerizable amphiphiles Polymerization of the ion pair amphiphiles is another approach that can be adopted to

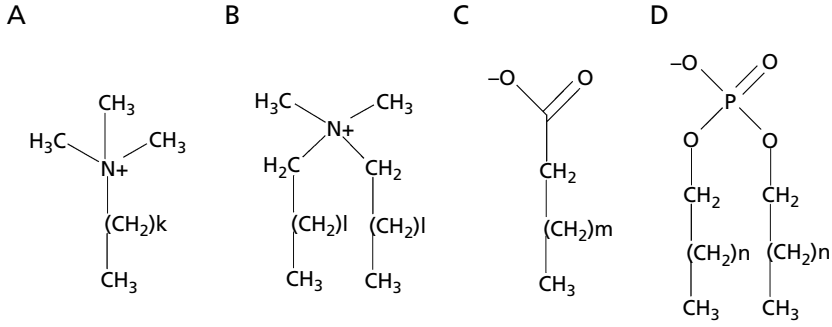


Figure 4 Structures of the amphiphiles used for ion-pair formation by Chung & Lee (1999).

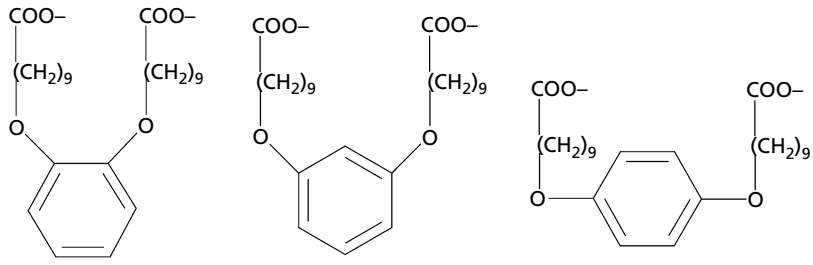


Figure 5 Structures of the bolaphiles that, together with two CTA^+, make the ion-pair amphiphiles used by Bhattacharya et al (1998).

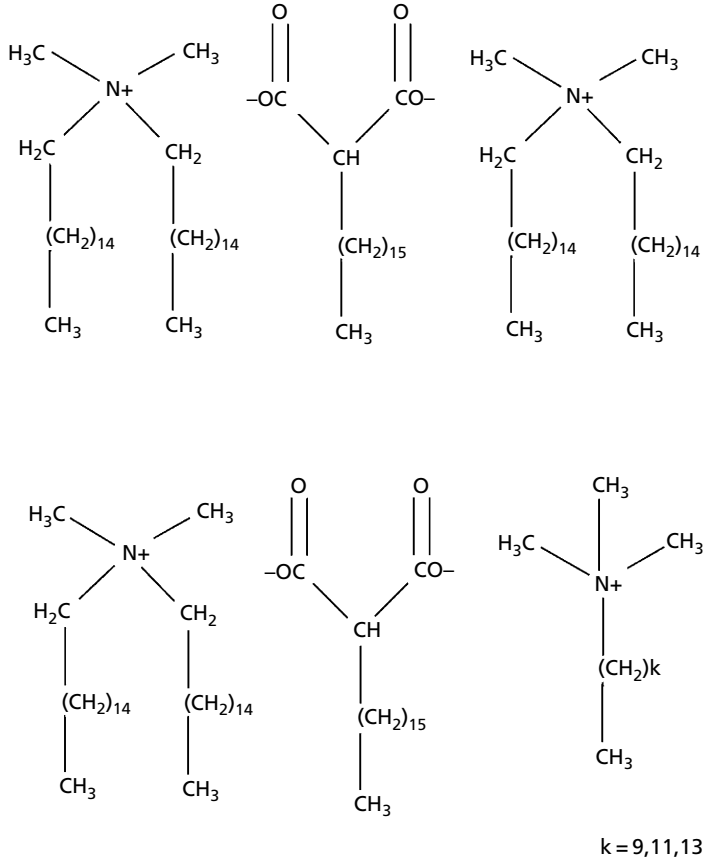


Figure 6 Structure of the pH-sensitive ion-pair amphiphiles used by Chung et al (2003a).

increase the encapsulation efficiency and the tightness of the bilayer membrane of the vesicles. Different ways of achieving polymerization of hydrated amphiphiles have been reviewed by Mueller & O'Brien (2002). Both single-chain amphiphiles (Hirano et al 1991; Morgan et al 1997; Chung & Chung 2002; Chung et al 2004a) and multichain amphiphiles have been polymerized (Chung & Chung 2002; Chung et al 2003b, 2004a, b). Polymerization can be achieved either by having an amphiphile containing a polymerizable group (Hirano et al 1991; Chung & Chung 2002; Chung et al 2003b, 2004a, b; Liu et al 2003), or by the addition of separate polymerizable monomers within the surfactant bilayer (Morgan et al 1997). The latter technique has mainly been used to produce hollow polymer spheres (McKelvey et al 2000; McKelvey & Kaler 2002), which will be presented below.

Hirano et al (1991) studied the vesicle stability after polymerization of the ion pair amphiphile *N,N*-dimethyl-*N*-octadecyl-*N*-[3-(1-acrylamido)propyl]ammonium stearate, the structure of which is displayed in Figure 7. The overall supramolecular structure was not significantly altered by the polymerization process and the fully polymerized vesicles showed an enhanced stability towards Triton X, NaCl and NaI. Morgan et al (1997) showed that, by incorporating a polymerizable monomer (in this case DVB) inside the vesicle bilayer of DTAB/SDBS, it was possible to retain the size of

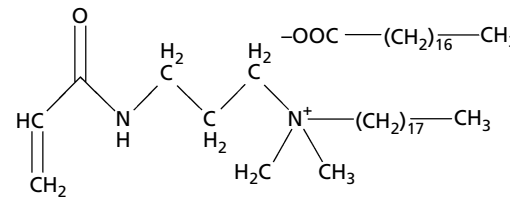


Figure 7 Structure of the polymerizable ion-pair amphiphile used by Hirano et al (1991).

the vesicles during dilution, and a resistance towards membrane disrupting agents was achieved. This was in direct contrast to non-polymerized DTAB/SDBS vesicles.

Chung & Chung (2002) tried polymerizing different combinations of ion-pair amphiphiles using an amphiphile with an ammonium head group and a carboxylate chain amphiphile with a lipoyl group at the chain end, to study the encapsulation and release of fluorescent markers. Only one of the IPAs, shown in Figure 8A, formed stable vesicles, which also showed a resistance to membrane disrupting surfactants (in this case SDS and Triton X-100) and ions. The encapsulating efficiency of CF and fluorescein isothiocyanate

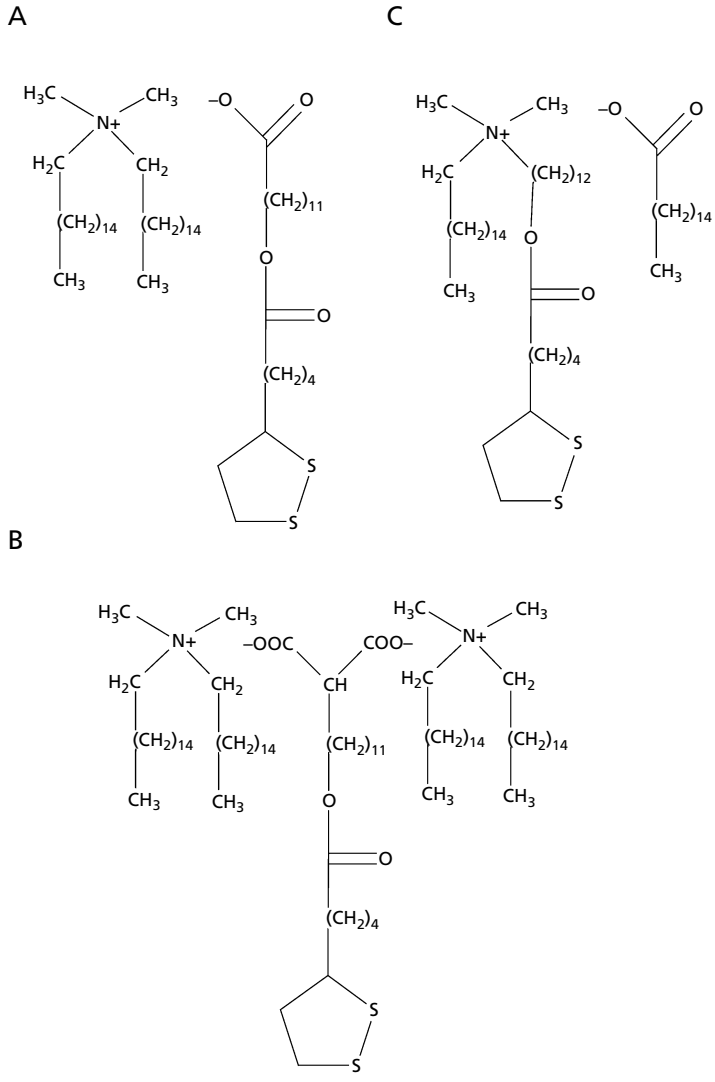


Figure 8 Structure of the polymerizable ion-pair amphiphiles used in the following references: Chung & Chung (2002); Chung et al (2003a, b, 2004a, b).

(FITC)-dextran was high and the release rate was very slow, such that just 20% of the FITC-dextran and 40% of the CF had been released after 5 days at 25°C. In a subsequent study (Chung et al 2003b), an anionic surfactant with two carboxylic groups was used with the same cationic surfactant as in the former study to control the ionic interaction between the head groups of the surfactants. The polymerized uncharged vesicles made from two ammonium and one dicarboxylated surfactants, shown in Figure 8B, showed an almost complete encapsulation of CF and FITC-dextran, while the negatively charged vesicles (made from one ammonium and one dicarboxylate surfactant) only partially encapsulated the fluorescence markers. The release was also different between the two vesicles, with the uncharged vesicle showing a much slower release than the negatively charged one. Chung et al (2004b) have also polymerized vesicles where the lipoyl group was in the two-tailed cationic surfactant instead of the carboxyl-containing single-chain surfactant, as shown in Figure 8C. The results were very similar to the earlier studies, with high encapsulation and slow release.

Polymerized vesicles that could be used for pH-sensitive release have also been studied (Chung et al 2004a); the amphiphiles are shown in Figure 9. The pH sensitivity was achieved by the deprotonation of the ammonium headgroup, which leads to a disintegration of the ion pairing and a partial collapse of the vesicle structure. CF was encapsulated and the release rate was faster at pH 11.5 than at pH 6 and 9.5.

Catanionic drug–surfactant complexes

In our research group at the Department of Pharmacy in Uppsala we have been working with catanionic complexes made from a surface-active drug and an oppositely charged surfactant. This is an interesting alternative to the encapsulation of drugs into catanionic vesicles that could be used for surface-active drugs. The integrity and the tightness of the vesicle membrane is not an issue since the drug is a part of the membrane. Another advantage is that complexes other than vesicles, such as micelles, could also be used for drug delivery purposes.

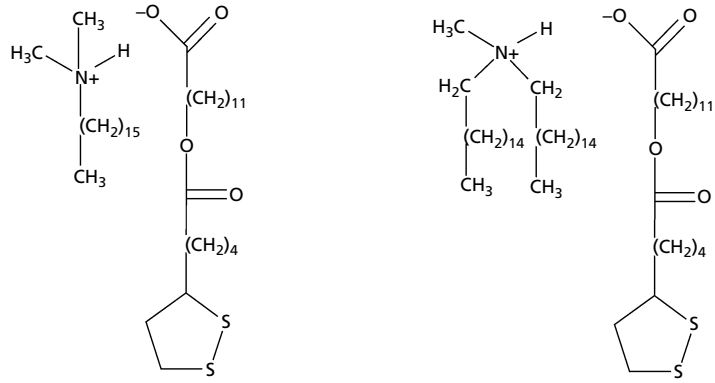


Figure 9 Structures of the polymerizable pH-sensitive ion-pair amphiphiles used by Chung et al (2004a).

Paulsson & Edsman (2001) discovered that surface-active drugs could form catanionic complexes when mixed with oppositely charged surfactant; it was later shown that this occurs quite frequently. In a study by Bramer et al (2006) five of the six systems investigated were able to form either catanionic vesicles, high viscosity micelles or both. The drug substances included in this investigation were chosen with the criteria that they were charged at physiological pH and had a structure that indicates surface activity. The substances investigated were naproxen, ibuprofen, lidocaine, orphenadrine, alprenolol and propranolol. These substances were mixed with oppositely charged amphiphiles in different ratios and the resultant phases were determined and studied. The systems included drug substances of both positive and negative charge at physiological pH. In several cases, cryo-transmission electron microscopy was used to image the structures formed in the catanionic systems, and to support the results obtained in visual and rheological studies. Examples of the systems investigated and of the type of complexes that were formed are presented in Figure 10.

Some systems have been studied in greater detail. For example, Bramer et al (2003) extensively investigated mixtures of SDS and the drugs diphenhydramine and tetracaine. Micelle and vesicle phases were found in both systems (see Figure 11). The pH and salt dependence in a

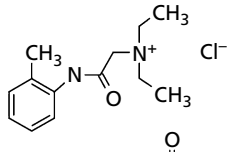
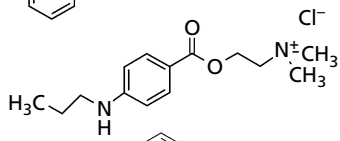
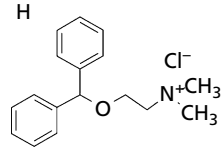
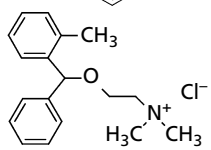
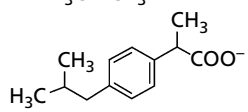
Drug substance	Oppositely charged surfactant	Type of complex/-es formed
 Lidocaine (hydrochloride salt)	SDS	Micelles
 Tetracaine (hydrochloride salt)	SDS	Vesicles and micelles
 Diphenhydramine (hydrochloride salt)	SDS	Vesicles and micelles
 Orphenadrine (hydrochloride salt)	SDS	Vesicles and micelles
 Ibuprofen (sodium salt)	BAC TTAB DoTAB	Micelles Micelles Micelles

Figure 10 Examples of drug substances and oppositely charged surfactants used to form catanionic complexes.

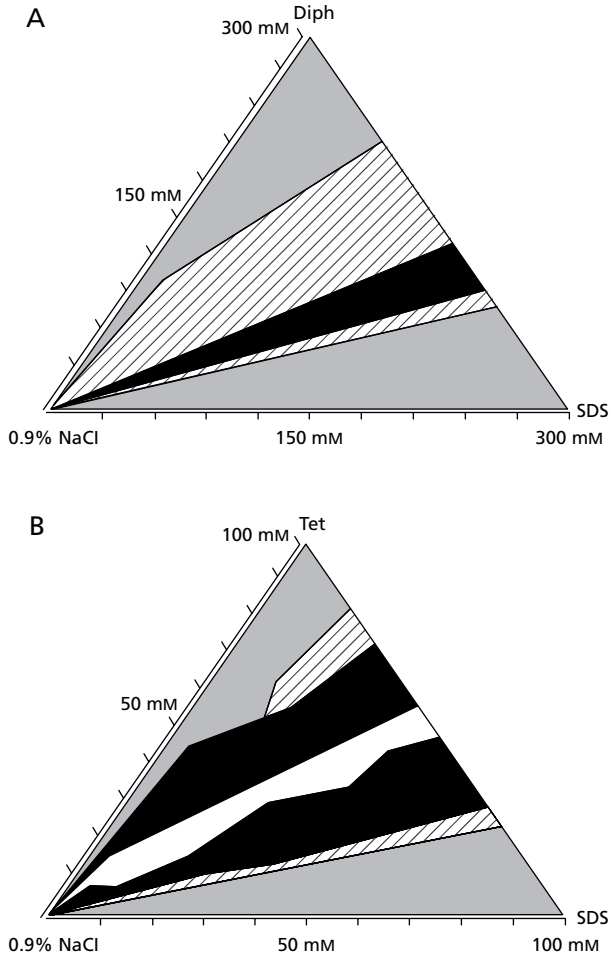


Figure 11 Phase diagrams redrawn from Bramer et al (2003). The white areas represent micellar/aqueous solution, the grey areas represent two-phase regions, the black areas represent precipitates and the striped areas represent the vesicle phase. The pH was left unadjusted when constructing both diagrams. A. Three-component system containing diphenhydramine (Diph), SDS and physiological sodium chloride solution. B. Three-component system containing tetracaine (Tet), SDS and physiological sodium chloride solution.

solution containing catanionic vesicles consisting of diphenhydramine and SDS were also studied and presented. The pH was varied between 0.5 and 10 and did not result in any notable changes. The salt concentrations were varied between 0.9 and 5.4%, but the addition of salt to the solution did not affect the vesicle phase until the concentration was at least 3.6%.

The drug release rate from catanionic aggregates incorporated in gels has been investigated for several different systems. A decrease of a factor of 10 to 100 in the diffusion coefficient, D, compared with the value obtained when the drug substance alone is incorporated in the gel, has been observed when the drug is incorporated in a catanionic complex within a gel matrix system (Paulsson & Edsman 2001; Östh et al 2002; Bramer et al 2003, 2006). One example of this is shown in Figure 12. The main mechanism behind this occurrence is most likely that the size of the micelles or vesicles

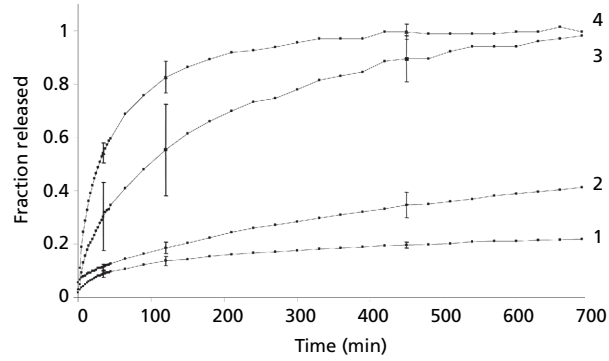


Figure 12 Release of orphenadrine from an agar-agar gel, redrawn from Bramer et al (2006). The release of orphenadrine is clearly prolonged when mixed with SDS, when the percentage of orphenadrine is: 30% of 160 mM (1), 40% of 40 mM (2) and 20% of 160 mM (3). The release from catanionic complexes incorporated in the gels is compared with a reference release for orphenadrine 96 mM (4).

formed is large enough compared with the mesh size of the gel matrix to prevent instant diffusion of the drug substance.

The effects of ionic strength and pH on two catanionic systems were studied in depth by Bramer et al (2007). Diphenhydramine (pK_a=9.0) and tetracaine (pK_a=8.5) mixed with SDS in different proportions were adjusted to different pH values and ionic strengths. The pH was varied between 8 and 11. In the diphenhydramine/SDS system, the vesicle and micelle regions were broadened at a higher pH, where the fraction of uncharged diphenhydramine increases and less substance is available to participate in catanionic interaction. The tetracaine/SDS system did not behave in a similar way; at pH 8 and pH 10 some of the vesicles changed into micelles on the SDS-rich side and when the pH was raised to 10 the vesicles turned into precipitates on the drug-rich side. The reason for the vesicle disappearance on the drug-rich side and not on the SDS-rich side was suggested to depend on differences in local pH. Viscosity measurements showed that the micelles decreased in size when the ionic strength was decreased and pH increased. The measurements were performed on micelle phases of the diphenhydramine/SDS system and the viscosity dropped by up to 3 times, caused by a decrease in the size or number of micelles, or both.

When the drug release from gels containing micelle or vesicle systems with an altered ionic strength or pH was studied, it was obvious that both factors affect the release rate, though the release can still be significantly sustained (Bramer et al 2007). A size change of micelles will give a change in release rate; vesicles, on the other hand, are of such a size that any changes that might have occurred would probably not be sufficient to affect the release rate.

Catanionic aggregates of diphenhydramine and SDS were also studied using electrodynamic methods, such as transient current measurements and dielectric spectroscopy (Brohede et al 2005). These methods can provide information about the concentrations and motion of drug molecules inside a gel matrix. Dielectric spectroscopy showed that the monomeric drug ions move unhindered inside the Carbopol gel, aggregates of comparatively small sizes were also present, but moved more slowly than the monomers. The transient current

measurements conducted failed to detect vesicles, as these are probably too large to move inside the gel and because they may have a net charge close to zero. Both diffusion coefficients from pure drug systems and from catanionic systems measured with electrodynamic methods compared well with measurements made with the US Pharmacopeia method.

The interactions between the drug containing catanionic complexes and the gel have been characterized and compared. For example, Paulsson & Edsman (2001) observed that amphiphilic drugs generally seem to increase both the elastic modulus, G′, and the viscous modulus, G″, of the gels. In all cases where rheological effects were observed, the gels still possessed rheological properties that are typical for gels. The release of fluvastatin from two different Carbopol gels, C934 and C1342, was compared, and the latter of these has a lipophilic modification. The release of drug from C1342 was slower than from C934, despite the fact that the vesicles were smaller in C1342. This difference could be due, in part, to different crosslinking densities, but mostly arises because of the lipophilic modification of C1342, which interacts with catanionic complexes in the vesicle phase formed by fluvastatin and the oppositely charged benzalkonium bromide. It has also been shown that pure drug substances interact with the gel matrix (Paulsson & Edsman 2002).

Catanionic complex–polymer interactions

Interactions between the catanionic complexes and polymers can lead to gel formation. Polymers can interact with the vesicle bilayer through hydrophobic interactions with the hydrophobic parts of the polymer (Ashbaugh et al 2002; Lee et al 2005; Medronho et al 2006), through electrostatic interactions in charged systems (Marques et al 1999a; Antunes et al 2004), or through a combination of both types of interaction (Marques et al 1999a; Antunes et al 2004). The interaction between the polymer and the amphiphile complex can induce structural changes in the amphiphilic complex (Marques et al 1999a; Regev et al 1999; Nilsson et al 2000; Antunes et al 2004; Lee et al 2005, 2006; Yan et al 2005). Systems where gels are formed by interaction between the vesicle or micelle and a polymer could be used for drug delivery, but as far as we are aware this has not yet been evaluated. Another application of these systems is as models for biological processes (Zhu et al 2006). In this section we briefly describe the research that has been published on polymer–vesicle systems.

Marques et al (1999a) studied the effect of oppositely charged polyelectrolytes in the SDS/DDAB system. Two hydroxyl ethyl cellulose derivatives were used, JR400 (molecular weight 500000) and the hydrophobically modified LM200 (molecular weight 100000). Owing to the increased screening of the electrostatic repulsion in the system, phase separations were observed at very low polymer concentrations. Structural changes were also observed in the vesicle shape, with faceted vesicles being formed in the presence of the polymer. In the presence of JR400, both faceted vesicles and small disc-like aggregates were observed; Figure 13 shows the structures that have been put forward for the gel phase. At high polymer concentrations, a gel-like viscoelastic phase occurred because of charge interactions between the negatively charged amphiphilic aggregates and the polymer. When using the hydrophobically modified polymer, in addition to the electrostatic interactions, the hydrophobic substituents can also interact with the vesicle bilayer. The structural effects on the vesicles and the formation of discs are further discussed by Regev et al (1999). In a later study of the same system, it was found that the crosslinks were more long lived for the highly charged hydrophilic polymer, but the number of crosslinks was higher for the less charged hydrophobic polymer (Antunes et al 2004). More marked changes were observed in the vesicle structure for the higher charged polyelectrolyte. The suggested mechanism for this was that a high-charge density polymer will affect the oppositely charged vesicle in two ways. First, the curvature of the surfactant film will be reduced on charge neutralization. Second, the conformational state of the surfactant alkyl chains can be changed as the Krafft point (i.e. the chain melting temperature) is strongly affected by electrolytes. The addition of a polyelectrolyte is expected to increase the melting

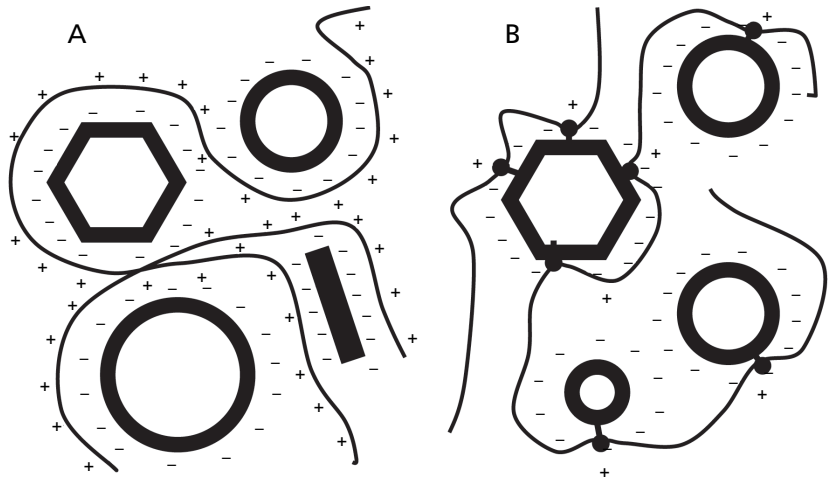


Figure 13 Schematic view of the possible structure for the gel-like samples, involving polymer–aggregate networks. A. The JR400 system, where mainly electrostatic interactions occur. Faceted and spherical vesicles are depicted, as well as disc-like aggregates (which are shown from an edge-on position). B. The LM200 system, where both hydrophobic and electrostatic interactions are present. This figure has been redrawn from Marques et al (1999a).

temperature and induce surfactant crystallization in the vesicles, which may lead to the formation of planar regions in the vesicles. The alternative mechanism suggested was that there could be an in-plane surfactant segregation induced by the polycation adsorption to the surface where there is a preferential interaction between the positively charged polyelectrolyte and the SDS. The heterogenous packing in the bilayer could induce morphological changes.

Ashbaugh et al (2002) also studied the DDAB/SDS system but they used a hydrophobically modified polyacrylate and compared the results with the SDBS/CTAT system. The positively charged vesicles precipitated with the addition of the polymer, but when the polymer was added to the negatively charged vesicles, it resulted in a single phase system that remained stable over several months. The length of the hydrophobic substituent was important, as a shorter substituent induced phase separation, indicating that the hydrophobic interactions must be strong enough to overcome the electrostatic repulsion between the polyelectrolyte and the vesicles. When the concentration of the vesicle and/or polyelectrolyte was sufficiently high, a gel formed. Both of the catanionic systems were similar, and it was suggested that the results may be generalized to other similarly charged mixtures.

Medronho et al (2006) studied the interaction between the uncharged hydrophobically modified poly(ethylene glycol) and both positively charged and negatively charged SDS/DDAB vesicles. In this system the interaction will solely be of hydrophobic nature and the rheological properties of the gels formed did not depend on the charge of the vesicles. The size of the vesicles was an important factor, as the viscosity and the elasticity increased for systems with larger vesicles. These researchers also found, as had Ashbaug et al (2002) previously, that the length of the hydrophobic modification affected the gel; a longer hydrophobic chain resulted in stronger polymer vesicle links.

Gel formation between hydrophobically modified chitosan and SDBS/CTAT vesicles has also been studied (Lee et al 2005). Precipitation occurred when mixing the polymer with oppositely charged vesicles, that is vesicles rich in the anionic surfactant; however, when mixed with positively charged vesicles at a high enough concentration, the sample transformed into an elastic gel. The onset of the gel formation required both a critical vesicle and a critical polymer concentration. The vesicles appeared to re-organize into smaller entities in the presence of the hydrophobically modified chitosan. The gel formation did not occur when using chitosan without the hydrophobic modification. The vesicle–polymer mixtures were later analysed using small-angle neutron scattering (Lee et al 2006). When low amounts of the hydrophobically modified chitosan were added to unilamellar vesicles (with a diameter ~120 nm), the vesicles decreased to approximately half their original size and, at a higher polymer/vesicle ratio, some vesicles became bilamellar and the sample contained both unilamellar and bilamellar vesicles. The authors suggested a mechanism for the changes that took place. At a low polymer concentration, only a few of the hydrophobic chains have been inserted into the vesicle membrane and the chitosan chains connect and network adjacent vesicles. The vesicle bilayer becomes more rigid as a result of the embedded polymer chains and this stabilizes a higher curvature of the vesicles, that is the vesicle size decreases. The addition of more polymer increases the number of chains embedded, as well as the connection between adjacent vesicles, until a limiting curvature is reached and the vesicles fuse into bilamellar structures with polymer chains that bridge the two bilayers. This system was later further developed by the same research group to mobilize and restrain vesicles using pH changes and enzymatic hydrolysis (Zhu et al 2006), resulting in a system that has similarities with biological processes involved in cellular communication. The vesicles can be restrained in the gel at neutral or basic conditions since the chitosan at neutral pH forms interpolymer associations that result in a strong insoluble network and the vesicles can be mobilized using chitosanase, which will hydrolyse the polymer network as shown in Figure 14.

Compaction/decompaction of DNA

The interaction between DNA and amphiphiles has been studied over a long period of time and, in the area of gene therapy, cationic lipids and liposomes have been used for

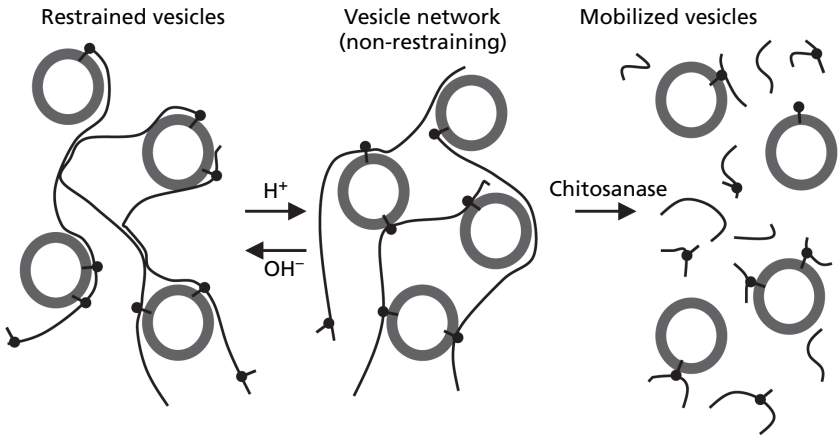


Figure 14 Bioinspired approach to the mobilization and restraint of vesicles. The vesicles are restrained by interpolymer associations, and interactions between the lipophilic modification of chitosan at a neutral to basic pH. The figure shows the vesicle network with its interaction between the chitosan and the vesicles at an acidic pH. The vesicles can be mobilized using chitosanase. Redrawn from Zhu et al (2006).

interactions with the DNA (see for example Yadava et al 2006). The uptake of DNA through the cellular membrane is facilitated by compaction, together with a reduction of the charge of the DNA molecule. Since the DNA molecule is negatively charged, the complexation of DNA using cationic lipids and polymers is a common approach (for a recent review see Collins 2006). Catanionic vesicles have recently been put forward as an optional way of accomplishing DNA delivery. Delivery of this kind relies on the same principles as are used in the more extensively studied traditional approach, using liposomes. Catanionic vesicle DNA delivery makes use of the interaction between the catanionic complexes and DNA for the compaction and decompaction (Mel'nikov et al 1999; Dias et al 2002b, c).

Mel'nikov et al (1999) studied DNA conformational dynamics in the presence of catanionic mixtures based on CTAB/SOS using a fluorescence microscopy technique, cryo-transmission electron microscopy, and by conducting diffusion studies. The conformational behaviour of individual DNA molecules was studied using a fluorescence marker. When adding DNA to negatively charged catanionic vesicles, no change in the conformational behaviour of the DNA molecule was detected. However, the addition of positively charged catanionic mixtures to the DNA solution resulted in a collapse of the individual DNA chains into a compact globular conformation, which adsorbed to the vesicle surface. It is known that, in the presence of CTAB alone, DNA exhibits a compact globular conformation and, by gradually adding SOS to such a sample, the CTAB-DNA complexes undergo a discrete globule–coil conformational transition. It was concluded that the interaction constant between the CTAB–SOS association is greater than that of the CTAB–DNA association and that decompaction is possible through the addition of negatively charged surfactants to the catanionic–DNA complexes.

In a later publication, Dias et al (2002c) studied the interaction between DNA and positively charged CTAB/SOS catanionic vesicles, with special attention being paid to the structure of the complexes formed. The formation of DNA–vesicle complexes was observed to start at 10^{-6} M DNA ($0.33\ \mu g\,mL^{-1}$). The complexes did not dissolve in an excess of DNA or surfactant, nor did they dissolve on dilution. The DNA–vesicle complexes coexisted with undisturbed vesicles until a DNA charge concentration [DNA] to net surfactant charge concentration [S+], [DNA]/[S+], of 1.3 was reached. The complexes were found to have a similar structure to that of other systems described in the literature, with the DNA molecules being ordered and packed between the amphiphile bilayers in the vesicle, as displayed in Figure 15. The inclusion of a negative amphiphile in the vesicle preparation seemed to induce denser packing of DNA in the complex.

In a subsequent study by Dias et al (2002b), the dissociation of the DNA–vesicle complexes was investigated further through the addition of the negatively charged surfactants SOS and SDS. SDS was more efficient at unfolding DNA than the shorter-chain surfactant, that is a smaller amount of surfactant was required to induce decompaction, and all the DNA was in a coil conformation, even at concentrations below the charge neutralization of the surfactants. Varying the chain length of the cationic surfactant did not affect the decompaction and the amount of negatively charged surfactant required to unfold DNA was independent of the hydrophobicity of the compacting amphiphiles CTAB, TTAB and DTAB. It was also observed that the phase diagram of the pure surfactant mixture could be used to predict the catanionic surfactant complexes formed after decompaction. This provides a method by which one can readily separate the amphiphiles used for compaction from the decompacted DNA. For example, when using cationic surfactants to compact DNA for purification purposes, the addition of a known amount of anionic surfactant could release the decompacted DNA back into the solution and, at the same time, form a precipitate with the oppositely charged surfactant.

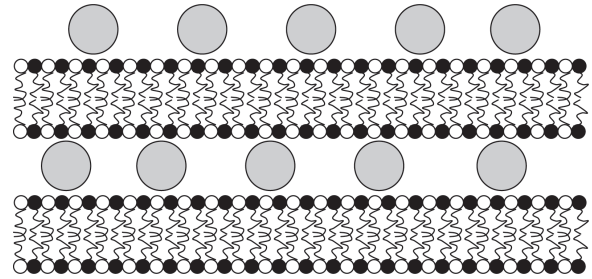


Figure 15 Schematic representation of the proposed structure for DNA–catanionic vesicle complexes.

The work on the interaction between DNA and catanionic complexes has been reviewed previously by the research group of Lindman (Dias et al 2002a, 2004; Lindman et al 2002; Miguel et al 2003).

Catanionic complexes as templates for synthesis

As mentioned in the section on polymerization of vesicles, the vesicles could be used as templates for the synthesis of spheres when a polymerizable monomer is included into the vesicle bilayer and these may be used for pharmaceutical applications in the future. The method developed by Morgan et al (1997) has been used for the synthesis of hollow polymer spheres (McKelvey et al 2000; McKelvey & Kaler 2002). Particles with an average radius of 60 nm and a shell thickness of 10 nm were made using styrene and divinyl benzene in the system CTAT/SDBS and CTAB/SOS (McKelvey et al 2000). Furthermore, it was possible to dry the particles completely and resuspend them in water without any apparent change in microstructure. The possibility of surface modification was also evaluated by sulfonation of the aromatic ring or by adsorption of surfactants to stabilize the particles. The particles were further characterized and the use of surfactants to stabilize the resuspended particles was studied in greater detail using small-angle neutron scattering (McKelvey & Kaler 2002). The polymer shell thickness was found to be 63 Å and the core radius was 560 Å. Since the presence of surfactants is necessary for redispersion of the hollow spheres, the use of polymerizable surfactants in the vesicles was investigated (Liu et al 2003). The polymerizable surfactants MUTB and MUBS (see Figure 16) both show two vesicle-containing regions in the phase diagram and one composition from each of the vesicle regions was polymerized. Several techniques were used to show that the vesicle structures had been successfully fixed by polymerization, with no intervesicle crosslinking. Silicone

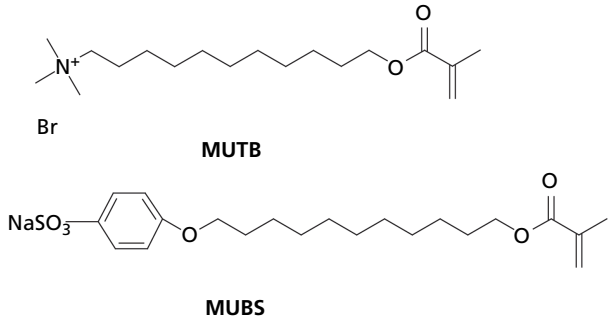


Figure 16 Chemical structures of the cationic surfactant MUTB and the anionic surfactant MUBS.

nanocapsules have also been synthesized using catanionic DTAB/SDBS vesicles (Kepczynski et al 2004). These capsules were filled with water, are densely crosslinked and non-porous and are therefore able to retain any water-soluble molecules on a long-term basis in their core.

Finally, it should be mentioned that catanionic aggregates could be used to grow inorganic nanostuctures, such as single crystal $BaWO_4$ nanowires (Shi et al 2002) and penniform $BaWO_4$ nanostructures using a block copolymer (PEG-b-PMMA) in catanionic reverse micelles formed from undecylic acid and decylamine (Shi et al 2003, 2006).

Catanionic assemblies with anti-HIV activity

Different analogues of galactosylceramide were synthesized and tested for anti-HIV activity and cytotoxicity (Blanzat et al 1999a, b). Several catanionic aggregates were tested and it was found that a gemini catanionic analogue (see Figure 17) possessed both a low toxicity and a strong anti-HIV activity. All the catanionic analogues showed typical phases for catanionic mixtures. The low toxicity of the gemini analogue compared with the other catanionic analogues was attributed to its unique aggregation characteristics (Blanzat et al 2003). Further studies using interactions between the analogue and phospholipids suggested that the gemini analogue would probably not penetrate into a biological membrane (Brun et al 2003). Blanzat et al (2002, 2005) have also developed a dendrimer

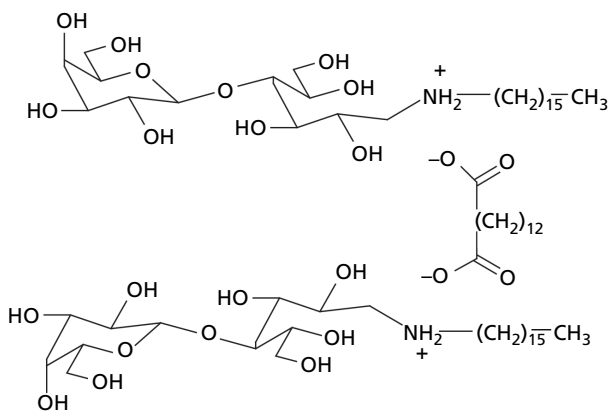


Figure 17 Structure of the gemini catanionic analogue of galactosylceramide.

complex based on hydrophobic and electrostatic interactions with the galactosylceramide analogue. The work conducted on the galactosylceramide analogues has been reviewed by Rico-Lattes et al (2005).

Concluding remarks

The use of surfactants will always raise the question of biocompatibility and toxicity because surfactants have a tendency to interact with biological membranes, proteins and enzymes. Depending on the intended usage of the catanionic complexes, for example the route of administration, the local toxicity problems will vary, for example mucous membranes are more sensitive to local irritation than the skin, and the alkyl chain length of the surfactant influences the toxicity. The surfactant class also affects the compatibility and, in general, the compatibility decreases in the order non-ionic – anionic – cationic. Sensitization has been shown to be a very small problem for anionic and non-ionic surfactants, while some cationic surfactants have proved to be allergenic. In general, the problem with local irritation and toxicity is a question of dose. See the reviews by Drobeck (1994) and Sterzel (1995, 1997) for more general information on toxicity problems associated with surfactants.

There have not been many biocompatibility studies made using catanionic systems, although some information was gained in a permeability study of a catanionic drug–surfactant complex. In that study, conducted by Östh et al (2002), the drug release from Carbopol gels was investigated using excised pig nasal mucosa. The drug substance diphenhydramine formed vesicles with SDS, was incorporated in the gels and then applied to the mucosa in an Ussing chamber for 210 min. A morphological microscopy examination showed that a lower concentration of SDS results in slightly less damage to the mucosa than a high concentration does. Initially, the high concentration of SDS resulted in activation of the cells but later it became disruptive, whereas the lower concentration inactivates the cells but disrupts them to a lesser extent. The nasal tissue was also exposed to unmodified Carbopol gels, as a control, which did not affect either the electrophysiology or the morphology of the mucosa. Another study has been made on a catanionic vesicle consisting of two oppositely charged surfactants. Kuo et al (2005) characterized the cytotoxicity of catanionic vesicles in RAW 264.7 murine macrophage-like cells. The catanionic vesicles consisted of SDS and hexadecyltrimethylammonium bromide (HTMA/DS), and cholesterol. The vesicles induced apoptosis in the macrophages and that was dependent on the cation (HTMAB), but not on SDS and cholesterol. Other cell lines (NIH/3T3 mouse fibroblast cells and BNL CL.2 mouse liver cells) did not undergo apoptosis.

One approach to overcome the biocompatibility issues would be to use low toxicity surfactants to make the catanionic aggregates. Rosa et al (2006) have shown that catanionic systems could also be made from positively charged amino acid-based compounds, for example ALA (arginine-*N*-lauroyl amide hydrochloride) and LAM (N^{α}-lauroyl-arginine-methyl ester hydrochloride) were combined with the negatively charged SOS, SCS and HS (sodium hydrogenated tallow glutamate). The surfactants LAM, ALA and HS proved to be better tolerated than conventional cationic surfactants in cell

viability tests. Vesicles were observed in the systems LAM/SCS, ALA/SCS, ALA/SOS and ALA/HS. These systems also produced rods, lamella, discs, cubosomes and hexosomes.

The field of catanionic complexes is a relatively recent one, which is growing, although the growth rate is not as fast as for example liposome-related research, which started approximately 20 years earlier. Since the review by Tondre & Caillet (2001) was published, an increasing number of publications have appeared. In 2001, the encapsulation efficiency and leakiness of the vesicles were issues, but since then multichain amphiphiles and the polymerization of the vesicles have improved the stability of the vesicles. Another approach available for surface-active drugs has been presented, where the drug is ion-paired with an oppositely charged surfactant, resulting in the drug forming part of the vesicle wall instead of being encapsulated in the vesicles. Several new applications have also been presented, such as the complexation of DNA using catanionic vesicles, and studies have appeared on gel formation in catanionic vesicle polymer systems that may show possible applications in the future. To the best of our knowledge, there are no publications on clinical studies, but this is probably because the area is still too young to have reached that phase. However, it would be surprising if none of the possible applications lead to success, with so many suggestions having been made so far in this growing field of research.

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