Development of surfactant coacervation in aqueous solution

Meina Wang and Yilin Wang*

Coacervation is a phenomenon in which a colloidal dispersion separates into two immiscible liquid phases: a liquid rich in colloidal phase in equilibrium with another diluted liquid phase. Surfactant coacervation here refers to coacervation whose main components are surfactants with low molecular weights. Over the past two decades, surfactants have been greatly developed and studies on coacervation in systems of novel surfactants have been reported. This review summarizes the development of coacervation occurring in monomeric surfactants, one-head and two-tail surfactants, gemini surfactants and their mixtures. The effects of surfactant molecular structure and external conditions on critical conditions for coacervation, structures of precursors and coacervates, and their relationships are described. The effects of inorganic salts, alcohols and organic salts on surfactant coacervation are also reviewed.

1. Introduction

Coacervation has attracted particular interest because of its widespread applications in water treatment,1,2 cosmetic formulation,3,4 protein purification,5,6 tissue elasticity,7 and pharmaceutical microencapsulation.8–10 Coacervation is defined as a process in which a colloidal dispersion separates into two immiscible liquid phases in the same solvent medium. The dense phase which is rich in colloidal components is called the coacervate, and it is in equilibrium with a relatively dilute liquid phase. The coacervate phase can remain as a turbid suspension of amorphous droplets or coalesce into a top or bottom liquid phase, depending on its density. Coacervation is a subtle balance of electrostatic interaction, hydrophobic associations, hydrogen bonds, van der Waals forces and other weak interactions. When these weak interactions are reduced, coacervation is suppressed, and when these weak interactions are enhanced, precipitation may occur. Coacervation can be divided into simple and complex coacervation on the basis of the coacervation mechanisms.11 Simple coacervation only involves one...
colloid species such as macromolecules or surfactants, and can be generated by adding a dehydrating agent such as salts or alcohols, or by increasing the temperature, which promotes inter-colloid interactions over the interaction of colloid species with solvent. Complex coacervation consists of at least two oppositely charged polyelectrolytes, biomacromolecules, surfactants and/or other colloid species, and is mainly driven by electrostatic attraction in the vicinity of electrical neutrality. Molecular structures, concentration, mixing ratio, ionic strength, pH, and temperature all affect the formation of complex coacervates. If classifying coacervation on the basis of the main components, coacervation can be divided into macromolecule coacervation and surfactant coacervation. Surfactant coacervation is the subject of this review.

Before reviewing surfactant coacervation, macromolecule coacervation will be briefly introduced because of its importance. Macromolecule-surfactant coacervation is a type of complex coacervation and is placed in macromolecule coacervation here. Macromolecule coacervation was first investigated by Bungenberg de Jong for the system of gum arabic–gelatin in 1920–1940s. He coined the term “coacervation” and defined the phenomenon. Then Oparin popularized coacervates in life science and proposed that life had originated in coacervates. Since then, macromolecule coacervation including synthesized polymers and natural biomacromolecules have been extensively studied, and experimental and theoretical investigations have been extensively reviewed by Dubin et al., Veis, Bohidar, Schmitt and Turgeon, and so on. Furthermore, macromolecule coacervation applied to microcapsule formation has also been reviewed. The works from Dubin et al., Burgess and Carless, and the works cited in the references have greatly promoted advancements in complex macromolecule coacervation. In particular, several theoretical models have been proposed by Voon et al., Veis et al., Nakajima and Sato, and Tainaka and have been compared in a review by Burgess. These theoretical models addressed the phase separation kinetics and described the driving forces, specific conditions and formation process for coacervation. The Voorn–Overbeek theory described how coacervation was a spontaneous process driven by electrostatic interaction and interpreted coacervation as a competition between electrostatic forces which tended to accumulate charged macromolecules and entropy effects which tended to disperse them. Veis et al. modified the Voorn–Overbeek theory and attempted to explain complex coacervation between two oppositely charged gelatins. The Veis theory is limited to systems with a low charge density and coacervation is thought to be driven by the gain in configurational entropy resulting from the formation of a randomly mixed coacervate phase. The Tainaka theory developed from the Veis theory is more general than the other theories and is applicable to both high and low charge density systems. This theory states that coacervation was driven by attractive forces among aggregates, which increased with the molecular weights and charge densities of macromolecules, and considered that the aggregates possibly became neutral prior to coacervation but without specific ion pairing.

Compared to macromolecule coacervation, fewer investigations have been carried out on surfactant coacervation without macromolecules. The main components of surfactant coacervation without macromolecules possess low molecular weights. Various surfactant systems generating coacervates have been reported. Although in principle coacervation can occur in other solvents, most of the surfactant coacervations reported take place in water. Considering that surfactant coacervation is a liquid–liquid phase separation in surfactant systems, surfactant coacervation can be classified into three types. One type is clouding phenomenon or lower consolute behavior – that is, phase separation upon heating for non-ionic surfactants or certain zwitterionic and ionic surfactants at high concentrations of inorganic and organic salts. The main driving force for this kind of coacervation is the entropy of water release from the head groups and alkyl chains of surfactants. Several excellent articles have reviewed the formation and applications of clouding phenomenon in surfactant systems. The other two types of surfactant coacervations do not occur when the temperature changes. One of them usually takes place in mixtures of oppositely charged surfactants, and no droplets are observed but two liquid phases are formed upon quiescence. This type of surfactant coacervation is normally called an aqueous surfactant two-phase system (ASTP) instead of surfactant coacervation. Its main driving force is a combination of the entropy of counterion release and water release. In another situation, oily droplets are usually observed in phase separation and the coacervate phase presents a sponge-like structure. The term “coacervate” is also called: “L3 phase”, “anomalous phase”, or “sponge phase”. The last type of liquid–liquid phase separation in surfactant systems is the most characteristic surfactant coacervation and the term “surfactant coacervation” is most often used for it. Therefore, this review mainly summarizes the advances in the last type of surfactant coacervation over the past 20 years, whereas the other two types of surfactant coacervations are only discussed briefly.

Early studies on surfactant coacervation were basically limited to the use of traditional monomeric surfactants and one-head and two-tail surfactants upon addition of different kinds of additives or oppositely charged surfactants. In recent years, along with the development of surfactants, novel surfactant coacervation has emerged and gemini surfactant coacervation becomes very attractive. In contrast to traditional surfactants, gemini surfactants can often generate coacervation by themselves without any additives. Thus, this review will include three sections: coacervation of single surfactants without additives, coacervation of surfactants with additives (alcohols, inorganic salts and organic salts), and coacervation of mixed surfactants. In each section, the studies on monomeric surfactants, one-head and two-tail surfactants, and gemini surfactants will be discussed. The main conclusions and a brief review of future perspectives are presented at the end. Although surfactant coacervation has a broad scope, this mini review is limited. So we apologise to the many contributors to the field whose works are not mentioned here.
2. Coacervation of single surfactants

In this paper, coacervation of single surfactants refers to the coacervation occurring in a surfactant solution without the second component. Coacervation in an aqueous solution is inherently associated with efficient dehydration in the colloid self-assembly process. The extent of dehydration of surfactants is dependent on their amphiphilic characteristic. Hydrophobic interaction between alkyl chains promotes intermolecular association of surfactants, enhancing the dehydration of surfactants. But polar and charged hydrophilic head groups prefer to be hydrated at the interface of the surfactant aggregates and water. Normally, surfactant coacervation should result from a combination of weak electrostatic repulsion between the hydrophilic head groups and a strong hydrophobic attraction between alkyl chains, which leads, because of efficient dehydration, to a condensed aggregate. However, if the dehydration is too strong, coacervation will be replaced by precipitation. A proper balance between dehydration and hydration is required to form coacervates.

2.1. Monomeric surfactants

Monomeric surfactants are the most widely applied traditional surfactants. Each of them contains one hydrophilic moiety chemically attached to one hydrophobic alkyl chain. Monomeric surfactants can be subdivided into ionic, non-ionic, and zwitterionic surfactants according to the charge properties of the hydrophilic head groups. Monomeric surfactant molecules usually aggregate into micelles when the concentration is above their critical micelle concentration. These micelles are homodisperse in aqueous solution and stabilized by their surface charges and hydration shell. Thus, a single monomeric surfactant cannot normally self-assemble into coacervates at room temperature.

Upon heating above a threshold temperature, aqueous solutions of non-ionic or zwitterionic surfactant micelles exhibit clouding phenomena, forming two co-existing isotropic phases. The threshold temperature is called the cloud point or precipitation. A proper balance between dehydration and hydration is required to form coacervates.

2.2. Gemini surfactants

Gemini surfactants are made of two amphilic moieties connected by a spacer group at the level of the head groups. So far, most coacervations for single gemini surfactants reported took place in a series of zwitterionic gemini surfactants with different lengths of alkyl chains. The synthesis and characterization of these surfactants were performed by Menger et al., and their systematic studies revealed that the formation of coacervates is mainly controlled by the length and symmetry of the two hydrophobic chains of the zwitterionic geminis. A “structural phase diagram” was constructed with the length values of the two hydrophobic chains (A and B) for 42 gemini surfactants at concentration of 5–50 mg mL\(^{-1}\) at 25 °C (Fig. 1a).

Four main zones were identified as gels, micelles, coacervates, and vesicles. Coacervates form when the chain lengths are intermediate (8–12) and the two chains are identical or close to each other (e.g., A8B10, A10B10). For the surfactants with two alkyl chains of similar length, the shorter or longer chains (e.g., A8B8 or A14B16) lead to small micelles or vesicles. When the alkyl chains are quite dissymmetric (e.g., A18B8, A8B18), gels predominate, with an interconnected network of vesicle-sized particles. Apparently the self-assembled aggregates are so sensitive to the chains that A8B10 and A10B8 only form coacervates and micelles, respectively, because the two chains exchange their locations. Remarkably, the images from cryogenic temperature high-resolution scanning electron

![Fig. 1 Coacervation of zwitterionic gemini surfactants. (a) Structural phase diagram of 42 zwitterionic geminis; (b) light microscopy image (top) and cryo–HRSEM images (middle) of A8B10 coacervate droplets, cryo–HRSEM images of fractured A8B10 coacervate droplets (bottom); (c) cryo–HRSEM image of branched zwitterionic geminis; (d) proposed schematic illustrations of zwitterionic surfactant coacervates. Adapted with permission from ref. 51, 53, 56 and 57. Copyright: American Chemical Society.](image-url)
microscopy (cryo-HRSEM) showed that the micron-sized spherical coacervate droplets in these systems exhibit a distinct sponge-like framework occupying the entire volume of the phase (Fig. 1b). This sponge-like structure is made of randomly connected bilayers, locally resembling the topology of a bicontinuous cubic phase, but displaying short-range order. Moreover, the coacervate phase of surfactants, in equilibrium with a dilute surfactant phase, is enhanced by increasing the amount of surfactant but is insensitive to extra water. The two phases are in a thermodynamic equilibrium. In addition, the coacervates of the zwitterionic gemini surfactants show salt tolerance because of their inner salt structure.

Thereafter, Menger et al.\textsuperscript{57} further synthesized a family of branched-chain zwitterionic geminics with different carbon numbers on the main alkyl chains \((n = 9, 10, 18)\), and found that coacervation takes place in aqueous solution of the geminis with the intermediate main alkyl chain \((n = 10)\) (Fig. 1c). Slightly decreasing the main hydrophobic chain length by only one ethylene \((n = 9)\) suppresses coacervates and generates vesicles, while increasing \(n\) to 18 induces gels. Menger proposed that such sensitivity of the zwitterionic gemini surfactant coacervation to the length and symmetry of the two hydrophobic chains can be understood in terms of the negative Gaussian curvature of the monolayers forming bilayers. The Gaussian curvature \((H_0)\) of monolayers forming bilayers is defined by \(H_0 = 1/R_o\), where \(R_o\) is the spontaneous radius of curvature. When \(H_0\) is close to zero, surfactants self-assemble into a lamellar structure. When \(H_0\) is positive, surfactant monolayers are curved to water, and the monolayers prefer to break into micelles. When \(H_0\) is slightly negative, surfactant bilayers fuse with each other and transfer to a disordered sponge-like phase, \textit{i.e.}, coacervates (Fig. 1d). Hyde et al.\textsuperscript{49} stated that if a negative Gaussian curvature is desirable for the surfactant bilayer, the critical packing parameter of the surfactant should be larger than one, which means that the hydrophobic domain of the surfactant must be bulky compared with its hydrophilic head groups. This is a necessary requirement for the molecular shape for surfactants to form coacervates. Dozens of the zwitterionic gemini surfactants can self-assemble into coacervates without variation of environmental conditions just because they meet the requirement of molecular shape for coacervation to occur. In addition, for the zwitterionic gemini surfactants, the hydrophilic part probably adopts an alternating “\(+-\)(\(+-)\)” arrangement in the adsorbed monolayer of aggregates triggered by electrostatic attraction between opposite charges. The efficient packing of hydrophilic parts endows the zwitterionic surfactants with the ability of self-assembling into bilayers. The two alkyl chains with intermediate or identical length yield proper hydrophobic interaction and flexibility in the bilayers, which induce coacervates instead of micelles and vesicles.

Besides zwitterionic surfactants, some non-ionic gemini surfactants also exhibit coacervation phenomenon without increasing temperature. Whether non-ionic gemini surfactants can form coacervates depends on the nature of hydrophobic head groups. Imura et al.\textsuperscript{58} reported an occurrence of simple coacervation in a single “natural” glycolipid biosurfactant, 4-O-(4′,6′-di-O-acetyl-2′,3′-di-O-alkanoyl-β-D-mannopyranosyl)-D-erythritol (MEL-A), and found that the absence of the 4′-O-acetyl group leads to a slight decrease in spontaneous curvature and induces a drastic aggregate transition from coacervates to vesicles (Fig. 2a).

Our group\textsuperscript{60} reported that a pH-sensitive carboxylic gemini surfactant, 4,8-dioctyl-3,9-diosoxy-4,8-diaza-1,11-undecanedicarboxylate (SDUC) forms an oily phase (coacervate) in aqueous solutions at a pH of around 4.0, whereas it forms vesicles at a higher pH. The decreased electrostatic repulsion and increased hydrogen bonding among the carboxylic groups of SDUC at the lower pH are responsible for the coacervation from the fusion of vesicles. Therefore a strong electrostatic repulsion between the head groups of ionic gemini surfactants prevents coacervation. However, Niu et al.\textsuperscript{64} found that cationic gemini surfactants with diethylammonium head groups and diamido spacers form vesicles at lower concentrations, and the vesicles aggregate into coacervates with increasing concentration (Fig. 2b). Transmission electron micrographs (TEM) indicate that the coacervates exhibit both sponge and vesicle-like structures. The formation of coacervates is probably caused by the adhesion and fusion of vesicles at high concentrations by hydrogen-bonding between the diamido spacers of the surfactants. Therefore, introducing additional weak attractive interactions such as hydrogen bonds and \(\pi-\pi\) stacking can assist coacervation in single surfactant systems.

As described previously, the structural nature of hydrophobic chains and hydrophilic head groups of surfactants are the key controlling factors of surfactant coacervation. In addition, the formation of single surfactant coacervation is also affected by counterions. Jaeger et al.\textsuperscript{65} observed coacervation in...
a shamrock surfactant with iodide counterions (CH$_3$)$_3$N$^+$[CH$_2$)$_{12}$N$^-$[CH$_2$)$_{12}$N$^-$[CH$_2$)$_{12}$N$^-$[CH$_2$)$_{3}$3I$^-$. This was attributed to the fact that iodide ions bind more effectively than chloride ions to the cationic surfactant head groups.

3. Coacervation of surfactants with additives

Although some single surfactants can generate coacervation, generally surfactant coacervation occurs with the aid of additives. Inorganic salts, alcohols and organic salts are the most often used additives to help the formation of coacervates.

3.1. Coacervation of surfactants with inorganic salts

3.1.1 Monomeric surfactants. Surfactant coacervation with inorganic salts was first observed in mixtures of a long chain cationic surfactant Hyamine® 1622 with different kinds of monovalent or polyvalent inorganic salts. It was found that the surfactant coacervation depends on the concentration, hydrated radii, and valency of salts. There is a critical salt concentration above which coacervation can occur, while below it the surfactant solution is homogeneous. The critical salt concentrations in a 3% Hyamine® 1622 solution were found to be 0.027 M for KSCN, 0.059 M for KClO$_3$, 0.064 M for NaBr, 0.067 M for NaN$_2$, 0.320 M for NaCl, 0.079 M for Cu(NO$_3$)$_2$, and 0.430 M for CuCl$_2$. The binding of salts with ionic surfactants induces growth and fusion of surfactant aggregates through screening electrostatic repulsion between the ionic head groups of the surfactant. A small increment of salts induces tremendous growth of the micelles before coacervation. As reported, at concentrations above the critical salt concentration, the homogeneous solution of Hyamine® 1622 separates into two liquid phases over a wide range of concentrations. The volume of coacervate phase decreases with increasing concentration of salts and is proportional to $A + B/C^{1/2} + D/C^{3/2}$, where $A$, $B$ and $D$ are constants and $C$ is the concentration of added salts. At very high salt concentrations of several moles, the surfactant colloidal species start to precipitate instead of coacervate.

Surfactant coacervates show a characteristic specificity to the counterions of added salts. The cationic Hyamine® 1622 systems described previously are sensitive to anions, whereas the surfactant coacervations of anionic soap systems, including alkali oleates, stearates and palmitates, are sensitive to cations. The effectiveness of surfactant coacervation follows a Hofmeister series or lyotropic series for monovalent counterions and is enhanced with an increase of the valency. The stronger the binding of counterions to ionic surfactants, the more effective the shielding of the electrostatic repulsion among the ionic head groups, and then coacervation is preferred more.

3.1.2 One-head and two-tail surfactants. The microstructures of coacervates and the aggregates prior to coacervation are associated with the nature of surfactants. For the one-head and two-tail negatively charged surfactant Aerosol OT (AOT) reported by Menger and Sykes, AOT in aqueous solution self-assembles into vesicles and the vesicles change into coacervates by introducing alkali metals (Cs$^+$, K$^+$, Li$^+$, Na$^+$, Rb$^+$). Although the AOT coacervate was previously observed by Acharya et al., Menger and Sykes did more thorough work on the system. The coacervate was rationalized in terms of positive-to-negative changes in the spontaneous mean curvature (H$_0$) of the AOT bilayers, which was caused by decreased electrostatic repulsion among the AOT head groups. The critical parameters of the AOT coacervation in the presence of the alkali metal salts were determined. At a fixed salt concentration, the coacervate volume increases linearly with the AOT concentration. Furthermore, the coacervate phase contains a high content of water but is immiscible with the dilute aqueous phase. It was found that a coacervate of 0.2 M AOT and 0.3 M NaCl in water is immiscible with 0.3 M NaCl in water. This is attributed to the enthalpic requirements for breaking up the three-dimensional sponge-like AOT structure of the coacervates. A similar microstructure of surfactant aggregates prior to conversion to coacervates was also observed by Giokas et al. Polymerized vesicle coacervates were achieved in a cationic ammonium one-head and two-tail bromide surfactant, (4-carboxybenzyl)bis[2-(10-undecenoyoxy)ethyl]methylammonium bromide by ultraviolet excitation in a wide range of potassium chloride levels.

3.2. Coacervation of surfactants with alcohols

3.2.1 Monomeric surfactants. Surfactant coacervates induced by alcohols are commonly L$_3$ or sponge phase, and are directly related to their concentration and molar ratio. Alcohols in surfactant coacervation are usually pentanol or hexanol. When alcohols have been added to surfactant solutions, coacervation has been found in non-ionic surfactants, zwitterionic surfactants, and ionic surfactants with excess salt. In surfactant/alcohol/water ternary phase diagrams, the two-phase region is usually observed on either side of the L$_3$ phase: L$_3$/L$_{ab}$ (lamellar phase) region and L$_3$/L$_4$ (isotropic phase) region. In Fig. 3, Hoffmann et al. mapped out the phase diagrams of the ternary system, zwitterionic surfactant tetradecyl(dimethyl)ammonium oxide (C$_{14}$DMAO), heptanol and water. The two-phase L$_3$/L$_{ab}$ region is defined as between the L$_3$ phase and the lamellar L$_{ab}$ phase, and covers a large surfactant and alcohol concentration range, but only over an extremely narrow alcohol/surfactant ratio. The freeze fracture transmission electron images (FF-TEM) of the L$_3$ phase showed a sponge-like structure with more or less a network of ordered curved bilayers.

The formation of the coacervate phase (L$_3$) is dependent on the alkyl chain length of the alcohols. A previous work of Hoffmann et al. demonstrated the higher homologous alcohols than hexanol cannot cause the L$_3$ phase. In a chapter about the L$_3$ phase, Beck and Hoffmann, pointed out that the L$_3$ phase is very sensitive to ionic charges, and it becomes unstable when a few percent of neutral surfactants are replaced by ionic surfactants in the surfactant/alcohol systems. For most ionic surfactant/alcohol systems, the L$_3$ phase may form when the head group charges of the surfactant molecules are sufficiently shielded by excess salt. For examples, Strecker et al. observed the
TEM images of the L₃ phase at different C₁₄DMAO/heptanol concentrations (right): (a) 50 mM/110 mM, (b) 70 mM/135 mM, (c) 100 mM/185 mM, and (d) 70 mM/135 mM in which the L₄ phase exists. Adapted with permission from ref. 70. Copyright: American Chemical Society.

L₃ phase in a ternary system of cetylpyridinium chloride/heptanol/NaCl in water. Hoffmann et al. found the L₃ phase in the system of calcium dodecyl sulfate (CDS)/alcohol in water, where CDS behaves like a non-ionic or double-chain surfactant because of the binding of calcium ions with dodecyl sulfate ions.

Compared with the hydrocarbon alcohols discussed previously, perfluorinated alcohols are much more effective in inducing surfactant coacervation. Khaledi et al. showed that a small percentage of a perfluorinated alcohol induces coacervation in aqueous media for a broad range of surfactants with diverse molecular structures and compositions (Table 1).

3.2.2 One-head and two-tail surfactants. A phospholipid is a typical one-head and two-tail surfactant. If alcohols are used as its solvent while water or electrolyte solutions are used as its nonsolvent, mixing of phospholipid/alcohol solutions with water can yield coacervation. Ishii et al. pointed out it is important to simple coacervation of phospholipids that the solvent and nonsolvent are mutually miscible. Batzri and Korn applied coacervation to prepare single-bilayer liposomes by injecting an ethanolic solution of phospholipid into water. Saegusa and Ishii investigated the effects of alcohols (methanol, ethanol, and 1-propanol) and salts (sodium chloride and calcium chloride) on simple coacervation in the system of phospholipid/alcohol/water, and found that phospholipid forms coacervates when ethanol is used as a solvent, but forms a transparent highly viscous gel when methanol or 1-propanol is used instead. Furthermore, a larger volume of water phase is required to induce the phospholipid coacervation with 1-propanol in comparison with methanol or ethanol.

3.3. Coacervation of surfactants with organic salts

Unlike inorganic salts or alcohols, organic salts simultaneously display electrostatic and hydrophobic interactions with oppositely charged surfactants. The occurrence of coacervation in surfactant/organic salt systems not only depends on the nature of the hydrophobic groups of organic salts but also relies on the geometry of organic salts.

3.3.1 Monomeric surfactants. Jiang et al. studied the phase behaviors of aqueous mixtures of dodecyltrimethylammonium bromide (DTAB) with a series of sodium oligooarene sulfonates (POSn), where n is the number of charges on the sulfonate, and observed coacervates with green fluorescence in the mixtures of DTAB with POS4 or POS6 at the charge neutralization point (Fig. 4). The coacervates were suppressed when POS4 or POS6 were replaced by less charged POS2 or POS3. The surface tension and small angle neutron scattering results indicated that POS4 and POS6 show the features of polyelectrolytes while interacting with DTAB. The formation of coacervates can be understood in terms of the construction of zwitterionic oligomeric surfactant analogues through

Table 1 Perfluoro-alcohol/acid induced surfactant coacervation systems²

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<thead>
<tr>
<th>Group</th>
<th>Anionic amphiphile</th>
<th>Cationic surfactant</th>
<th>Coacurator</th>
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<tr>
<td>(A) Complex perfluoro-alcohol/acid induced coacervates</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Sodium alkane sulfates: SDS, SHS, SOS, DBSA</td>
<td>DTAB, CTAB, OTAB</td>
<td>TFE, HFIP, TFA, PFPA, HFBA</td>
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<tr>
<td>2</td>
<td>Phospholipids: DPPG</td>
<td>DTAB, CTAB</td>
<td>HFIP</td>
</tr>
<tr>
<td>3</td>
<td>Bile acid salts: SC, SDC</td>
<td>DTAB, CTAB</td>
<td>TFE, HFIP, TFA,</td>
</tr>
<tr>
<td>4</td>
<td>Perfluorinated surfactant: PFOA</td>
<td>CTAB</td>
<td>HFIP</td>
</tr>
<tr>
<td>(B) Simple perfluoro-alcohol induced coacervates</td>
<td></td>
<td></td>
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<tr>
<td>5</td>
<td>Zwitterionic surfactant: DMMAPS</td>
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<tr>
<td>6</td>
<td>Zwitterionic phospholipid: DPPG</td>
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<tr>
<td>7</td>
<td>Anionic phospholipid: DPPG</td>
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<tr>
<td>8</td>
<td>Cationic surfactants: DTAB, CTAB</td>
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<tr>
<td>9</td>
<td>Anionic surfactants: SDS + HCl</td>
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<tr>
<td>10</td>
<td>Non-ionic surfactants: Triton X-100, Triton X-114</td>
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electrostatic and hydrophobic interaction between DTAB and the oligomeric salts. When mixing DTAB with other dyes including tartrazine, amaranth, carmoisine, or erythrosine, coacervation also takes place.

Bendito et al.\textsuperscript{80} reported that tetrabutylammonium ions (Bu$_4$N$^+$) lead to surfactant coacervation in vesicular solutions of ionic surfactants alkyl carboxylic acids (alkyl = octyl, decyl, dodecyl, and tetradecyl) and oleic acids. These alkyl carboxylic acids form vesicles at pH near their apparent pK$_a$ where the deprotonated/protonated species are at a stoichiometric molar ratio. By increasing the Bu$_4$N$^+$ concentration, the vesicles form coacervates and the coacervation region is very wide (carboxylic acid/Bu$_4$N$^+$ molar ratio from 0.3 to 10). In the coacervation, Bu$_4$N$^+$ accelerates the suspensions of alkyl carboxylic acid/carboxylate mixtures because of its salting-in feature. Electrostatic attraction and hydrogen bonds are established in addition to hydrophobic interaction in the hydrocarbon region. In particular, one or two butyl groups of each Bu$_4$N$^+$ may stretch outside the polar shell of the alkyl carboxylic acid vesicles because of the steric restriction, whereas the rest of the butyl groups of Bu$_4$N$^+$ may connect with the butyl groups of other Bu$_4$N$^+$ molecules in the same or different vesicles. The continuous crosslinking among the Bu$_4$N$^+$ molecules bridges the vesicles. As the Bu$_4$N$^+$ concentration increases, more and more vesicles are connected, finally leading to the occurrence of coacervation. Similarly to Bu$_4$N$^+$, the cationic organic salt, benzyltriphenylphosphonium chloride, with four benzene rings, at a very low concentration of 1 mM can also induce coacervation in an aqueous solution (0.1–0.5 mM) of SDS.\textsuperscript{82} In addition to the interactions mentioned previously, in this system π–π interaction plays an important role in connecting the different surfactant aggregates in coacervation.

Considering practical applications of surfactant coacervation in food and life science, biocompatible bile salts have been widely used.\textsuperscript{83–87} Almgren et al.\textsuperscript{83} reported the phase behavior of CTAB with the bile salt SDC (NaDOC), and found that a coacervation region (Fig. 5a) exists in the L$_1$ phase (micelle phase) as opposed to the L$_a$ (lamellar phase) phase in the dilute surfactant area. The area of the two L$_1$-type fluid phases is elongated and almost symmetrically located near the equimolar ratio of the two oppositely charged compounds. The charged neutralized coacervates are proved to be built up by a three-dimensional network of interwoven, thread-like aggregates. The interwoven thread-like microstructure instead of the sponge structure probably resulted from the rigid steroid skeleton of SDC. The polar face of SDC is oriented toward the bulk solution, but its nonpolar face is placed towards the micelle core, and the SDC molecules incorporate in the CTAB aggregates and force the head groups of CTAB apart. This situation favors the formation of highly curved aggregates. Replacing CTAB by other alkyltrimethylammonium bromides (C$_n$TAB, C$_4$TAB, and C$_{12}$TAB), the aggregation and phase separation of the mixtures with SDC displays similar situations.

Panda et al.\textsuperscript{86} investigated the effect of the nature of bile salts on the phase behavior of alkyltrimethylammonium bromides (C$_n$TAB) with different alkyl chain lengths (n = 12, 14, 16). All the C$_n$TAB–sodium cholate (SC) mixtures only form a clear isotropic phase, while all the C$_n$TAB–SDC mixtures can form coacervates. Among them, the mixtures of C$_n$TAB (n = 14, 16) with SDC exhibit a transition from rodlike micelles to

![Fig. 4 Phase separation (right) and phase diagram (left) in aqueous mixtures of DTAB and sodium oligoarene sulfonate: POS4 at room temperature. Adapted with permission from ref. 79. Copyright: American Chemical Society.](image-url)
coacervates, but the C_{12}TAB–SDC mixture does not form rodlike micelles before coacervation. The different phase behaviors of C_{n}TAB with SC and SDC can be understood from the location of the bile salts at the micelle/water interface where SC with one more hydroxyl group is much closer to the bulk solution.

3.3.2 Gemini surfactants. Gemini surfactants possess a much stronger ability to form coacervates because of their dimeric amphiphilic structure. The investigation on the phase behavior of cationic gemini surfactant hexamethylene 1,6-bis(dodecyldimethylammonium bromide) (C_{12}C_{6}C_{12}Br_{2}) with bile salt sodium cholate (SC) in dilute solution indicated that coacervate phase coexists with L_{a} or crystal phase in the equivalent mixture (Fig. 5b). The SC molecules inserted in the surfactant aggregates were demonstrated to exist as dimers because of hydrogen bonds between the three hydroxyl groups. Compared with a monomeric surfactant, the coacervation in the mixture of gemini surfactant with SC is probably promoted by stronger electrostatic and hydrophobic interactions in the SC dimers and the dimeric structures of gemini surfactants. However, the coacervates cannot be separated from lamella and crystals in the whole concentration range studied.

Our group achieved a separate coacervate phase by the interaction of the same cationic ammonium gemini surfactant with sodium benzoate (NaBz) in aqueous solution. The formation of coacervates was found to depend mainly on the NaBz and C_{12}C_{6}C_{12}Br_{2} concentrations and their molar ratio (Fig. 6). A critical NaBz concentration of at least 0.10 M is required to form coacervates. The amount of C_{12}C_{6}C_{12}Br_{2} required for coacervates is very small and covered a very wide concentration region. The phase boundaries of coacervation shift to higher C_{12}C_{6}C_{12}Br_{2} concentration with increasing NaBz concentration. The cryo-TEM and cryo-SEM results showed that the precursors of coacervation are long, dense and almost uncharged, thread-like micelles, and the coacervates are a three-dimensional layer-stack network structure formed by the assembly of thread-like micelles. The formation of coacervates can be rationalized from the variations of the electrostatic and hydrophobic interactions of C_{12}C_{6}C_{12}Br_{2} with NaBz and the resultant aggregate changes upon the increase of the C_{12}C_{6}C_{12}Br_{2} concentration. The enhanced electrostatic and hydrophobic interactions between NaBz and C_{12}C_{6}C_{12}Br_{2} bring about the micellar growth from small spherical to thread-like, and finally the interlacing of thread-like micelles leads to the three-dimensional dense network that is a coacervate.

By changing the hydrophilic part of the organic salt, our group constructed another coacervation system in which a pH-sensitive N-benzoylglutamic acid (H_{2}Bzglu) and C_{12}C_{6}C_{12}Br_{2} were used. As well as the H_{2}Bzglu and C_{12}C_{6}C_{12}Br_{2} concentrations and their molar ratio, the pH also significantly impacts on the formation of coacervates. The coacervates are formed when the H_{2}Bzglu species with one negative charge are dominated. A lower critical H_{2}Bzglu concentration of 0.03 M was required to form coacervates than that for NaBz. Here the H_{2}Bzglu molecules not only display electrostatic and hydrophobic interactions with C_{12}C_{6}C_{12}Br_{2} like NaBz, but also have hydrogen bonds between their carboxylic acids. The hydrogen bonds lead to the formation of H_{2}Bzglu oligomers. The double chains of C_{12}C_{6}C_{12}Br_{2} and the H_{2}Bzglu oligomers play the roles of connecting aggregates through multiple binding sites. These factors endow the mixture with a very high efficiency in generating coacervates.

4. Coacervation of mixed surfactants

Aqueous mixtures of oppositely charged surfactants have been widely employed to fabricate coacervates because of their strong electrostatic and hydrophobic interactions. As pointed out by Filipović-Vinceković et al. and Panda et al., coacervates in catanionic surfactant mixtures are normally generated at the charge neutralization point in the transition region from precipitates to micelles. Ghosh and Dey proved that the coacervates are 1 : 1 complexes in the mixture of sodium N-lauroylsarcosinate (SLS) and N-cetylpyridinium chloride (CPC). The surfactants were thought to form ion pairs in the coacervates. In each ion pair, two non-covalently attached alkyl chains are connected to a common pair of head groups bound through electrostatic interaction. The structure of the surfactant ion-pairs is similar to that of zwitterionic gemini surfactants.

The coacervate structures of mixed surfactants are significantly affected by the compositions of mixtures. Schulz et al. found that the dilute aqueous mixture of sodium 10-undecenoate (SUD)–DTAB has different precursors of coacervation in the opposite sides of the two-phase region. Rod-like micelles agglomerate into bundles in the DTAB-rich side of the region, whereas globular micelles agglomerate into clusters in the SUD-rich side.

However, when coacervation takes place in many cases of oppositely charged surfactants, no droplets are observed, but two liquid phases are observed upon quiescence. The
surfactants are usually richer in one phase than in another phase, but both phases are dilute. The two phases are formed by different kinds of aggregates. This type of coacervation is commonly described as an aqueous surfactant two-phase system (ASTP), as described in the introduction. The formation of ASTP in catanionic surfactant systems is strongly dependent on surfactant aggregates. On the basis of the aggregate structures formed in the surfactant-rich phase, ASTP can be separately induced by entanglement of rod-like micelles, formation of a lamellar phase, or dense packing of vesicles.38–40,96–100 Kaler et al.48 observed the entanglement of rod-like micelles in the surfactant-rich phase in catanionic mixtures of CTAB and sodium octyl sulfate (SOS). Huang et al.47 reported the microstructures of ASTP in the mixtures of dodecylpyridinium chloride (DPCl)/sodium laurate (SL) and DTAB/SL. The FF-TEM images proved that the upper and bottom phases are dense and sparse vesicles, respectively. Furthermore, Huang et al.48 investigated the effects of surfactant concentration, temperature, salt concentration and additives (octanol, toluene) on ASTP in DTAB/SL. They found that the addition of salt, octanol and toluene induces the phase separation, whereas increasing the temperature inhibits the phase separation. Furthermore, Huang et al.49 studied the ASTP behavior in an aqueous mixture of cationic gemini surfactant hexamethylene 1,6-bis(dodecylidenammonium bromide) \( (C_{12}H_{25}C_{12}Br_2(Et)) \) with SL, and revealed that the surfactant aggregates in the upper and bottom phases are lamellar structure and vesicles, respectively, and the aggregate structures are influenced by temperature and shearing. Similarly, lamellar structure was also observed by Hao et al.46 in the upper phase of the ASTP systems consisting of SL with tetradecyltrimethylammonium bromide (TTAB) or tetradecyltrimethylammonium hydroxide (TTOH).

5. Conclusions and perspectives

This short review summarizes the development of coacervation occurring in single surfactants, surfactants with inorganic salts, alcohols or organic salts, and surfactant mixtures. The surfactants involved include monomeric surfactants, one-head and two-tail surfactants, and gemini surfactants. The effects of surfactant molecular structures and external conditions on critical conditions for coacervation, structures of precursors and coacervates, and their relationships have been described. Surfactant coacervation requires that surfactant aggregates are close to electrical neutrality prior to coacervation. Surfactant coacervation can be controlled by charge density, alkyl chain length and number, concentration of surfactants, and molar ratio of surfactants to additives or oppositely charged surfactants. Surfactant coacervation can be induced by the entanglement of wormlike micelles, the crosslinkage of vesicles, the fusion of bilayers, and so on. Surfactant coacervates exhibit a sponge structure in most cases.

Even though a larger number of surfactant coacervations have been studied over the past few decades, further development of more efficient surfactant coacervation is expected because of the enormous practical needs for drug encapsulation, cosmetics, detergents, protein separation and so on. On the basis of the conclusions from the literature, introducing a larger number of intermolecular interaction types and sites will greatly improve the ability of surfactants to generate coacervation at lower concentration and with fewer components. Therefore, with the development of surfactants, gemini surfactants and the extended oligomeric surfactants provide tremendous potential for coacervation because of their structural diversity and their greater number of interacting groups. So far, the reports on coacervation of gemini and oligomeric surfactants are still quite scarce. Thus the coacervations produced by these novel surfactants deserve to be explored in the future. Searching for more efficient and functional organic additives to induce surfactant coacervation is another fascinating aspect in this field. Endowing additives with functions (such as drug and pigments) and multi-interacting sites will expand the applications and reduce the cost of surfactant coacervation.

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Notes and references
