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ARTICLE

Self-assembly of fatty acids: from foams to protocell vesicles

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Fatty acids are potentially versatile substitutes to phospholipids and synthetic surfactants in materials chemistry and biophysics. However, sodium (or potassium) salts of saturated long chain fatty acids (SLCFA) are long known to be soluble at high temperature but they crystallize below their Krafft point, hampering their use for multiple applications. Recent advances have shown that under particular experimental conditions, i.e., by using a ‘good’ counter-ion, SLCFA can be dispersed in water into various supramolecular assemblies what opens new fields of research and applications. Here, recent studies on the self-assembly of fatty acids are commented and some potential applications are proposed and discussed.

Introduction

Michel-Eugène Chevreul (1786-1889) was a French chemist and the first to introduce ‘fatty acids’ and the term ‘saponification’. It is now well known that fatty acids can be obtained from animal or vegetable oil (fat) by simple hydrolysis of their triglycerides. One can distinguish several classes of fatty acids amongst them are hydroxylated fatty acids, saturated fatty acids and unsaturated fatty acids (see figure 1). The later have been widely used and studied, mainly because of dietary properties but will not be commented much in this review. Here, it is considered that saturated long chain fatty acid (SLCFA) bear chain length higher than 12 carbons. The fatty acid alkyl chain length is of much importance since it determines the solubility in water, the longer the alkyl chain, the lower the solubility. The pH is also of strong importance since it determines in which state is the polar head of the fatty acid. The carboxylic COOH form may turn to a COO⁻ group at high pH in water, the latter being much more polar. The concentration may also drive the self-assembly, here we will focus on relatively high concentrations, at least above the well-known critical micellar concentration (CMC)¹. Then, aqueous dispersions of sodium and potassium salts of saturated long chain fatty acids (soaps) have been widely studied, mostly at the beginning of the XXth century by Mc Bain²⁻⁵. Later, various phase diagrams of mixtures between NaOH (or KOH) and SLCFA have been investigated⁶⁻¹⁰. In the following, except when mentioned, we consider only equimolar ratio between the base and the SLCFA, i.e., ‘pure’ soaps. In these conditions, the pH is determined by the mixture, i.e., the nature of the base (weak or strong). The main feature of the phase behaviour of sodium (or potassium) pure soaps is that they can be dispersed under the form of micelles at high temperature, above the Krafft point. Pure soaps are dissociated, forming pairs of positively charged metal (Na⁺) and negatively charged fatty acids that are well dispersed in water under

the form of micelles. At contrary, in ‘cold’ solutions, below the Krafft point, the same pure soaps crystallize depending on the alkyl chain length^{7,8}. Formation of fibers have also been reported¹¹. It has been proposed that this occurs because of the spontaneous reprotonation of carboxylate anions yielding the formation of undissociated fatty acids that can further complex with some remaining soaps¹². As commented later, this behavior depends on the nature of the counter-ion. The crystallization phenomenon has probably weakened the use and studies of SLCFA in water because physical-chemists like when surfactants are well dispersed at room temperature. Besides, crystals of fatty acids lack many properties that are exhibited by their soluble salts at high temperature. For instance, ‘hot’ solutions of sodium myristate exhibit good foaming properties, whereas crystals are poor foaming agents¹³.

Fatty acids (including SLCFA and other classes) have been successfully dispersed in water but in combination with other surfactants. Catanionic systems amongst which are binary mixtures of fatty acids and cationic surfactants have attracted researchers, mainly because these dispersions exhibit fascinating self-assembly properties¹⁴⁻¹⁷ and are also well foaming¹⁸. Other systems involve combination of palmitic acid with cholesterol¹⁹⁻²² or monoglycerides²³ which allow forming stable dispersions of SLCFA in water. However, it is only 10 years ago that successful dispersions of ‘pure’ SLCFA which no longer crystallize even when kept at 4°C have been obtained²⁴. This requires the use of what we can call ‘the good counter-ion’. Upon ion-pairing SLCFA with tetra-butyl ammonium hydroxide (TBAOH, then pure soaps TBA⁺/SLCFA⁻), these fatty acids were shown to be soluble, forming micelles, and no longer crystallized upon decreasing the temperature at 4°C for months, i.e., a temperature much lower than the Krafft point of the sodium soaps. It seems obvious that in such a case, SLCFA remain deprotonated whatever the temperature under the form of TBA⁺/SLCFA⁻ pairs and then, that uncharged pairs of fatty acid-counter-ion no longer form

preventing crystallization. Later, choline was also shown to be ‘a good counter-ion’ allowing formation of stable micelles when ion-paired with SLCFA^{25, 26}. Here again, crystallization no longer occurs when samples are kept at 4°C for long period (months). It has been also shown that sodium salts of SLCFA (again pure soaps) can be dispersed in water but upon addition of guanidine hydrochloride that allows preventing the crystallization²⁷. In that case, elongated micelles are formed at ‘high’ temperature which transit to flat membranes upon cooling. Here, it is expected that the guanidium counter-ion strongly binds to the SLCFA preventing reprotonation and further crystallization as commented above for TBAOH.

All these works opened an avenue for other studies on fatty acid self-assemblies and for their use as foaming agents or other applications. Here, the main advantage compared to ‘common’ surfactants is that SLCFA are bio-available, cheap, and green and can be obtained in large amounts. One fundamental domain in which SLCFA are of interest is that of the origin of life. Protocells are hypothetical structures which are precursors of the first cells. By analogy with modern cells, it is assumed that protocells were vesicles made of fatty acids because they were the most simple amphiphilic molecules that could be present in the prebiotic soup^{28, 29}. However, up to now, only vesicles made of unsaturated or short chain fatty acids have been built^{30, 31}. As commented later, using SLCFA (which could also be present in the prebiotic soup) should offer a more realistic model for protocells if one can build vesicles from the above mentioned dispersions.

Here, the various results obtained in the literature on such dispersions of fatty acids in water are commented and some perspectives in this field of research are proposed and discussed.

Stable dispersions of SLCFA

All mixtures commented hereafter were done in pure water and not buffers. Powders of SLCFA are generally weighted, water is added and next the counter-ion (generally liquid or previously prepared in water). Because SLCFA are solid powders at room temperature, samples have to be heated above their melting temperature and vigorously shaken to ensure homogeneity. The pH is then determined by the nature of the mixture. Upon ion-pairing with sodium or potassium (pure soaps), SLCFA form micelles at high temperature which further crystallize below the Krafft point of the corresponding SLCFA. Some other counter-ions yield similar results, i.e., the formation of micelles in hot solutions but still crystallization upon cooling^{32, 33}. This phenomenon of crystallization can be circumvented by employing what we further call ‘a good counter-ion’. Raoul Zana was the first to propose such a counter-ion^{24, 34}. He used tetrabutyl ammonium hydroxide (TBAOH, see figure 1) and observed that SLCFA with a chain length up to 24 carbons could be dispersed in water without crystallizing even when kept at 4°C for months. The TBA⁺ counter-ion probably very strongly interacts with SLCFA⁻ (that remain deprotonated) and prevents the reformation of protonated SLCFA and uncharged TBA-SLCFA pairs which would yield crystallization¹². Competition studies between sodium and that counter-ion should provide valuable information on this phenomenon. For instance, one could use sodium-myristate salt in water above the Krafft point (to

keep it soluble) and progressively add TBAOH to measure the competition interaction, using for instance isothermal titration calorimetry (ITC). Initial solutions were prepared by formulating equimolar mixtures of SLCFA and TBAOH, i.e., **pure soaps**, but varying the molar ratio between both these components should yield a different phase behavior. Such formulations could yield mixtures of TBA⁺/SLCFA⁻ and protonated SLCFA if it is in excess compared to the counter-ion. This is equivalent to decrease the pH which is around 10 for equimolar mixtures. Also, decreasing the pH of equimolar solutions upon addition of HCl should be of interest and could allow formation of SLCFA vesicles. Indeed, vesicles made of oleic acid are generally built by decreasing the pH of a micellar solution, i.e., from sodium oleate dispersions and this will be commented in the section dedicated to protocells.

The second counter-ion which allowed getting well dispersed SLCFA in water was choline (see figure 1)^{25, 26}. It has the strong advantage of being greener than TBAOH however; it is a very bad smelling molecule what should hamper its use for many applications. This counter-ion also allows formation of micelles that are stable at low temperature.

Sodium soaps of SLCFA have been fully dispersed in water but by using an additional compound named guanidine (see figure 1)²⁷. Guanidine is commercially available under the hydrochloride form (GuHCl) which dissociates in water into the guanidium and chloride ions. This counter-ion is particular compared to choline or even TBAOH since it brings it-self a counter-ion (Cl⁻). Then, for ion-pairing with fatty acids, sodium salts of SLCFA have to be used. In that case, the pH of the solutions is around 9.5. Then, in the mixtures, one always has aqueous Na⁺/Cl⁻ present in solution. An alternative to this would be to use guanidine acetate which is also commercially available. In combination with NH₃⁺ salts of SLCFA, it should yield ammonium, acetate, guanidium and SLCFA aqueous mixtures that can be lyophilized, eliminating ammonium acetate and yield the guanidium salt of SLCFA, i.e., a NaCl free mixture. Using GuHCl also allowed preventing the crystallization of SLCFA but the phase behavior was slightly different as that observed using TBAOH or choline. In that case, viscous isotropic solutions were obtained at high temperature and composed of elongated micelles³⁵. Upon cooling, turbid solutions made of flat stacked bilayers were obtained²⁷. For myristic acid, that transition occurred at about 21°C, a temperature much lower compared to that of the Krafft point (41°C). Similar observations were done for longer alkyl chains, e.g. palmitic and stearic chains. We initially observed at ‘high’ temperature the formation of entangled tubular structures which were called ‘anastomosis’²⁷ but such structures were artifacts because they were obtained for samples close to the phase transition, about 21°C for myristic acid, the temperature at which samples were prepared for microscopic observations. Small angle neutron scattering has further allowed demonstrating that elongated micelles indeed formed at high temperature. It is obvious that the guanidine moiety strongly interacts with the carboxylic group of SLCFA, preventing the crystallization. The electrostatic interaction is probably emphasized by bidentate interactions between both groups as already evidenced with phosphate or carboxylate and guanidium groups³⁶⁻³⁹. Here again, there is a lot to do by varying the pH, the molar ratio between

the guanidine and SLCFA in order to modify the phase behavior of these systems. Measuring the interaction of guanidine with SLCFA could also be performed by ITC as has been commented above in the case of TBAOH by pouring GuHCl in a 'hot' sodium myristate solution.

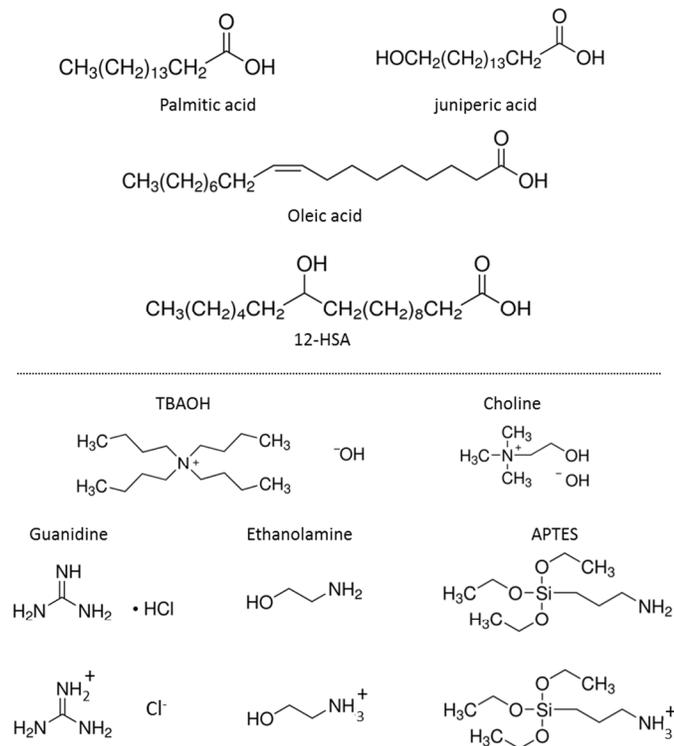


Figure 1. Chemical structures of fatty acids and counter-ions used in the different studies mentioned in the main text. Guanidine, ethanolamine and APTES are shown in their neutral and protonated forms.

There are very probably other counter-ions which could allow dispersing SLCFA in water and studies should be done in this sense since it could yield various phase behavior of interest for applications. SLCFA ion-paired with polylysine or other positively charged polymers should yield peculiar phase behaviors. Aminoclays⁴⁰ could also be of interest since SLCFA bilayers could intercalate between silica layers or SLCFA could ion-pair with these clays and be dispersed in water. In addition, aminopropyl triethoxy silane (APTES) which is used to synthesize amino-clays could also ion-pair with SLCFA⁴¹.

As previously commented, fatty acids can also be unsaturated and/or hydroxylated and some works have been done on the later class. Hydroxylated fatty acids are of particular interest because they can be extracted from agricultural resources. For instance, peels of fruits and legumes are made of such fatty acids⁴². There are some commercial hydroxylated fatty acids amongst which are juniperic acid (the omega-hydroxylated palmitic acid, WOHplm, see figure 1) and 12-hydroxystearic acid (12-HAS, fig. 1). The later has been widely used since it can form gels in oil and some apolar solvents⁴³. In water, it can be dispersed upon ion-pairing with ethanolamine as the counter-ion⁴⁴. It then forms tubular structures of about 10 μm length and 600 nm diameter which are composed by

several cylindrical stacked bilayers separated by a layer of water, the inner part of the tubes being water. These tubes exhibit a peculiar behavior upon heating since their diameter varies with the temperature⁴⁵ and they can also transit to twisted ribbons upon resting at room temperature⁴⁶. Additional details on the properties and self-assembly of such systems in water show their robustness^{47, 48}. Interestingly, ethanolamine is a weak base and then, these tubular dispersions have a pH of about 8.5 and are stable at low temperature. Comparatively, ethanolamine salts of SLCFA crystallize when kept at 4°C⁴⁹. This fatty acid can also be dispersed upon addition of NaOH and GuHCl, also forming tubes³⁵. Juniperic acid is also of interest and has a bola-lipid structure⁵⁰⁻⁵². It can be dispersed in water as flat membranes⁴⁹ which form conic structures upon dilution⁵³.

Using SLCFA but also hydroxylated fatty acids combined with TBAOH, ethanolamine or guanidine, foaming and emulsifying properties of these fatty acids have been studied as commented here after.

Stable dispersions for various applications

Stable dispersions as obtained in the above section allow using SLCFA for various applications and one started some experiments by studying foams and emulsions made of such fatty acids^{33, 35}. This has also been studied in the case of hydroxylated fatty acids⁵⁴ and reviewed recently⁵⁵. We focus here on the foaming properties of tubular structures made of 12-HSA. That fatty acid exhibits very good interfacial properties because it has a long alkyl chain and hydrogen bonds via the hydroxyl groups on the mid-chain that stabilize the fatty acid film deposited at the interface^{56, 57}. However, pure 12-HSA is not soluble in water and does not foam but by finding a way to disperse it in water, it has allowed to study its foaming capacities⁵⁸. It yields ultra-stable foams which do not get destabilized after six months at room temperature. This is because the interfacial film is very stable, that the fatty acid is weakly soluble in water and then remains either at the interface or in tubular structures but not free in bulk. Moreover, drainage is also slower because of the presence of tubes that get confined in the small spaces between bubbles (known as the Plateau region). However, 12-HSA foams can be easily destroyed upon heating above a given temperature that corresponds to a transition at which tubes melt into micelles in the bulk⁴⁴. At that high temperature, 12-HSA can exchange more easily and rapidly from the interface to the micelles and is also probably more soluble as free monomers in bulk. Moreover, micelles are much smaller than are tubes and do not slower drainage anymore, yielding destabilization of the film. Fatty acid formulations are then of particular interest as foaming agents and also as emulsifier but other applications could be developed in the future. Some assemblies of fatty acids have been proposed as vectors for drug delivery^{21, 22} but they are pH dependent and in any case precipitate at low pH. This can be of interest for controlled release experiments but not for drug delivery applications in animals. Animal skins are also rich in fatty acids and stable aqueous dispersions could be used for spreading at the surface of the skin⁵⁹. Juniperic acid has also been used for stabilizing gold nanoparticles⁶⁰

and may exhibit interesting self-assembly properties because of its bola-form.

One domain of particular interest is that of ‘templates’. Templates are defined here as self-assembled surfactants that form peculiar structures on which polymers can be deposited or monomers can be polymerized. Surfactants are then removed and the final polymeric material has the shape of the initial surfactant assembly (see figure 2). Here, this is of particular interest since fatty acids are available in large amounts and are cheap. The concept is schematized figure 2 showing how a fatty acid assembly (in red) can be used for such a task. This allows synthesizing materials of various forms and nature but most studies have been developed by using synthetic surfactants⁶¹⁻⁷⁰. In the case of fatty acid dispersions, the synthesis of the material can be triggered via electrostatic interactions. For instance, APTES seems promising at least as primer for initiating the polymerization.

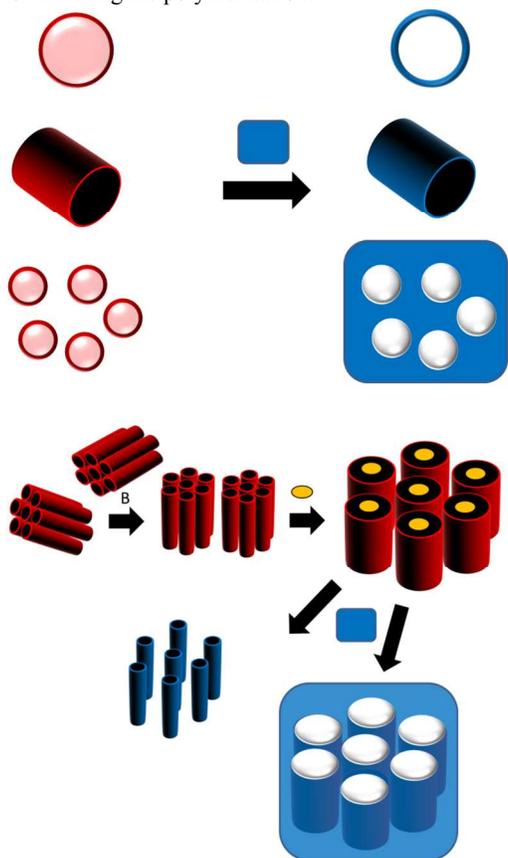


Figure 2. Schematically representation of the templating method. From top to bottom in the case of fatty acid vesicles (or an emulsion droplet), for tubular structures, for building a macroporous material and finally, from fatty acid hexagonal phases which self-orient in a magnetic field, B, and can be swollen upon addition of oil (yellow circle). In all cases, the self-assembled fatty acid structures are shown in red and the resulting polymer is shown in blue.

There exists another method for building hollow spheres or macroporous silica materials by using SLCFA emulsions as templates instead of aqueous self-assembled dispersions. The SLCFA are not initially dispersed in water but here, one takes advantage that such fatty acids under their carboxylic form (COOH) are soluble in apolar oil, for instance, hexadecane. Addition of water does yield stable emulsions only if a base is added in water. It allows

deprotonation of SLCFA which then migrate at the interface, stabilizing oil droplets. SLCFA exhibits in that case auto-emulsifying properties since simple hand-shaking allows formation of stable emulsions. High internal phase emulsions (HIPEs) can also be built by this way. Then, one can also take advantage that tetraethoxysilane (TEOS), the precursor of silicate-based materials, is also soluble in oil. TEOS and SLCFA have been mixed in oil and emulsions were built upon addition of water and ethanolamine. That base serves to stabilize the emulsion but also to hydrolyze TEOS which can further condense. Depending on the ratio between water, oil and TEOS, hollow spheres or macroporous materials were synthesized (figure 3). This method should be developed further for the synthesis of other materials.

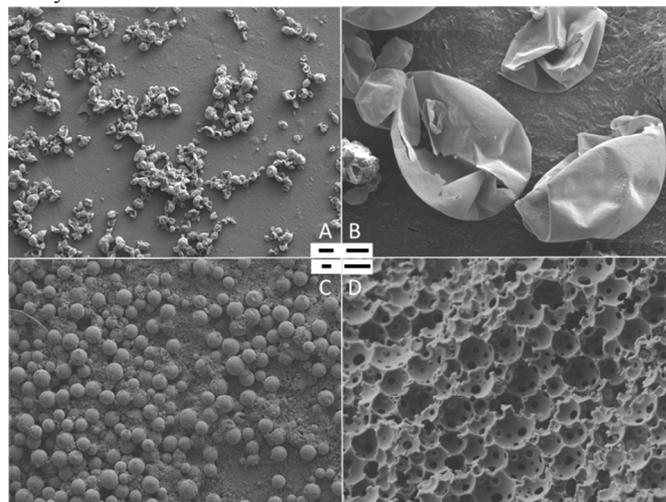


Figure 3. Silica hollow spheres and macroporous materials obtained from fatty acid emulsions. All images were obtained by MEB. These materials were obtained by co-solubilization of palmitic acid, TEOS and hexadecane. Then, water and ethanolamine were added and emulsions were built via vigorous hand shaking. A and B) For a 20% oil emulsion in water with 2% TEOS in oil yielding fragile hollow spheres that easily break. C) Same mixtures but with 20% TEOS allowing formation of more stable hollow spheres. D) HIPE formed by 90% oil in water and 50% TEOS in oil. The scale bar stands for 10 μm for B and D and 100 μm for A and C.

Another way for producing materials is to use liquid crystalline phases. For instance, hexagonal phases can be doped and it has been shown that such phases can accommodate a large amount of oil⁷¹⁻⁷³. The apolar oil allows swelling the hydrophobic region of the hexagonal cylinders (see figure 2). Then, polymerization of materials within the core of the cylinders became possible. Various SLCFA and TBAOH or ethanolamine mixtures self-assemble into hexagonal phases at high concentrations. The advantage here is that oriented materials can be obtained in a magnetic field⁷⁴⁻⁷⁶. One observed that upon heating the hexagonal phase, it transits to a micellar phase. Cooling in the magnetic field allows obtaining oriented materials in which the long axis of the cylinders is oriented parallel to the magnetic field (fig. 2). Such phases were also successfully doped with hexadecane (oil) and polymerization of materials within the core of the oriented cylinders should allow building oriented macroporous materials (fig. 2).

SLCFA vesicles, the formation of which is commented in the following section may also be of interest for building hollow polymeric spheres and we suggest below some ways to obtain them.

Towards more realistic protocell models

Protocells are defined as precursors of the first cells present on the early Earth. They were sacs allowing encapsulation of the prebiotic ingredients which further yield living cells. There are several models of protocells amongst which are fatty acid vesicles. Fatty acids were the most simple amphiphilic molecules which could be present in the prebiotic soup, either generated via prebiotic chemistry⁷⁷ or from extraterrestrial sources^{78, 79}. The first protocell vesicles made of fatty acids were built using oleic acid, an unsaturated fatty acid^{30, 80} (see figure 1). Later, short chain fatty acids, e.g., decanoic acid³¹ or other unsaturated fatty acids⁸¹ have been shown to form vesicles in solution. Such systems have been widely used to build protocell models^{28, 82-97}. However, any unsaturated fatty acids should have been oxidized by high dose of ultraviolet radiation present at the surface of the early Earth. Moreover, formation of double bonds is difficult to account in the initial prebiotic high temperature conditions. Short chain fatty acids form vesicles but only at high concentrations, for instance above 100 mM for decanoic acid. This may be a strong constraint since ingredients were probably much diluted in the prebiotic soup. For these reasons, SLCFA are more likely candidates as amphiphilic molecules for forming protocell because they should form vesicles at much lower concentrations. However, as described above, such fatty acids were known to crystallize, hampering the formation of stable vesicles, and then, their use as protocells. The recent findings on the stable dispersions of SLCFA using choline, TBAOH or guanidine open an opportunity for building stable vesicles made of SLCFA. The procedure for building such SLCFA vesicles could be similar to that used for short chain or unsaturated fatty acids, i.e., by decreasing the pH or upon addition of alkanols and we are exploring this avenue in the future. Further works should be done using the above mentioned counter-ions and also others such as diamines⁷⁸ which were more probably present in the prebiotic soup.

Other models of protocells involve membrane free droplets made of coascervates⁹⁸. A system has been recently developed using polyelectrolytes such as mixtures of peptides and nucleotides⁹⁹. Coascervates results from liquid-liquid phase separation of the components into materials-rich droplets of various sizes. Interestingly, surfactants are also known to yield phase separation and it is known as the clouding point¹ and it has been shown to occur for fatty acids¹⁰⁰. Further investigations in SLCFA systems should allow finding experimental conditions for which they would cloud and form SLCFA rich droplets that could also be good models of protocells.

Conclusions and perspectives

Fatty acids are of particular interest because they represent potential green and cheap surfactants available in large amounts. The use of saturated long chain fatty acids has long been hampered by the fact that they were known to crystallize in water below their Krafft point.

The recent findings which allow stably dispersing them in water open new fields of research. The excellent foaming and emulsifying properties of fatty acids make them good candidates as surfactants. Since they exhibit a rich polymorphism, they are also of interest as templates. One promising fundamental interest is probably that of protocells since SLCFA vesicles should offer more robust models. The successful dispersion of SLCFA in water has been achieved only 10 years ago and the preliminary works seem promising. Further systems should be explored to disperse SLCFA in water. Other counter-ions should be found in the future but also mixtures should be investigated. The pH, saline conditions, temperature... are experimental factors to be investigated. Since SLCFA are components of modern living cells, dispersing them in water should also be of interest in other domains such as biochemistry and bacteriology. For instance, *Acholeplasmae* are bacteria (class mollicutes) which are not capable of synthesizing their own lipids but can load fatty acids from the outer medium. Feeding such bacteria with stable dispersions of SLCFA is now possible and it should be investigated in the future. Finally, they are a lot of proteins such as lipid transfer proteins or enzymes (P450) which may interact with saturated long chain fatty acids. Again, stable dispersions of such fatty acids could be further used to study the interactions with these proteins.

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Figure TOC

Stable aqueous dispersions of fatty acids can now be obtained
and should yield multiple applications

