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Inverting structures: from micelles via emulsions to internally self-assembled water and oil continuous nanocarriers

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Abstract

Fluid-like colloidal structures are key components in nature's own functional materials and important for various applications. For instance, self-assembled structures are formed spontaneously by amphiphilic molecules in solvent, tailored by directional noncovalent intermolecular forces. These structures form the framework of cells defining their geometry and microenvironments for chemical reactions, for maintaining concentration gradients, and for nutrient exchange. Knowledge on the mechanisms at play that underlie the self-assembly of amphiphilic molecules into nanostructures in aqueous and nonaqueous solvents and their dispersion into particles can have direct implications for the rational design of new advanced and nature-inspired materials. These colloidal materials could help to deliver drug molecules and nutrients in a tailored manner to the body, or act as sustainable solvents for chemical or biotechnological processes. This contribution summarizes the recent progress in understanding the self-assembly structure formation in polar and nonpolar solvents and discusses the advances in hierarchically organized systems. Furthermore, it discusses challenges in the characterization of structure and dynamics in these biomimetic materials and highlights selected applications in the fields of drug delivery, food, and biotechnology.

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Reverse structures, Micelles, Emulsions, Microemulsions, Internally self-assembled particles, Self-assembly, Nanocarriers.

Introduction

In colloid and interface science, one is confronted with structures on different length scales from nanometers to microns [1]. The structural understanding of fluid-like colloidal structures in both aqueous and nonaqueous solvents can unlock some of the key questions in fundamental biology and colloid chemistry. These materials also have great potential for industrial applications, for instance, as functional hydrophobic coatings on medical devices, functional food materials, or as sustainable solvents for chemical or biotechnological processes [2–5]. This contribution summarizes the recent progress in deciphering the self-assembly of amphiphilic molecules in nonaqueous solvents as compared self-assembly in aqueous solvents and advances in the design of hierarchically organized emulsions, integrating the thermodynamic and kinetic domains. We highlight some challenges in the field devoted to studying supramolecular structures in nonaqueous solvents and close by discussing the potential applications of these soft materials in food and biotechnology.

Self-assembled structures

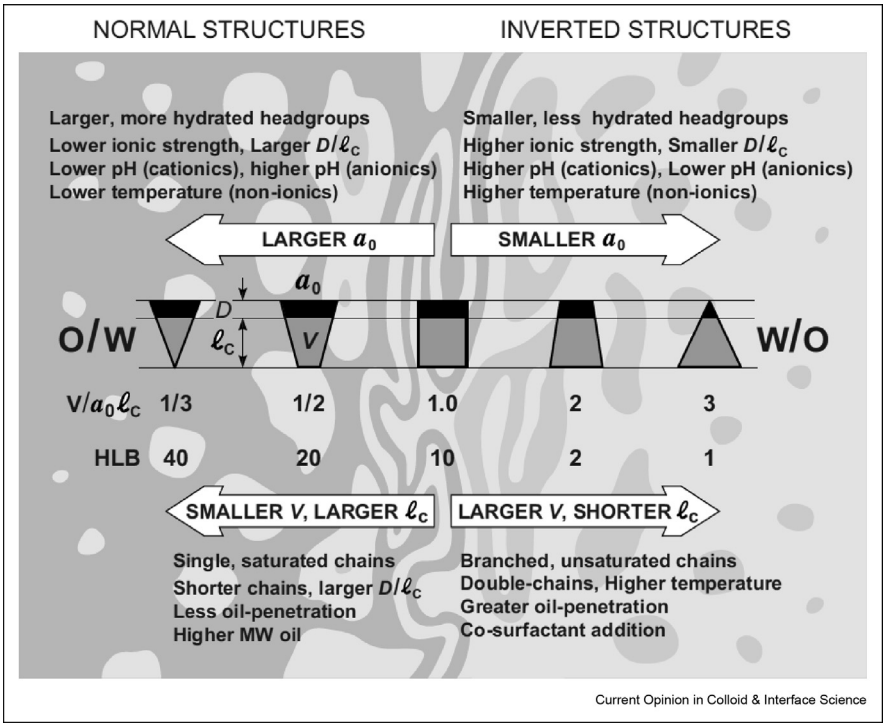
Self-assembled structures are the key features of living organisms. Layers of amphiphilic molecules such as phospholipids are the building blocks of cell membranes. Amphiphilic molecules are composed of hydrophobic moieties (e.g. hydrocarbon chains) and hydrophilic headgroups (e.g. carboxylic or glycerol functional groups) that are covalently linked together. In the solvent, these molecules self-assemble into supramolecular structures held together by noncovalent intermolecular forces. They include the van der Waals, hydrophobic, hydrogen bonding, and electrostatic forces, and the molecular geometry plays an important role in modulating the structural features [6]. In water, hydrogen bonding and the hydrophobic effect are particularly relevant interactions steering the structure formation. The hydrophobic forces, which are mostly of entropic nature, have been suggested as the strongest intermolecular forces driving the self-assembly of amphiphilic molecules. However, in nonaqueous environments, the hydrophobic forces are absent, and, depending on the type of solvent, hydrogen bonding interactions may be limited.

Micelles

Self-assembled structures such as micelles are formed by amphiphilic molecules in a solvent above the critical micelle concentration (CMC) [6] and above the Krafft temperature [1]. In most applications, the solvent is water and such micelles are just called micelles or 'normal' [7] or 'regular' micelles as opposed to 'inverted' [6] or 'reverse' micelles which are formed in nonpolar liquids. The possible structure of the aggregates includes spherical, cylindrical, or lamellar geometries, depending on the interaction forces between the molecules and geometry of the hydrophilic part (headgroup) and of the hydrophobic part (tail) of the amphiphile. The critical packing parameter (CPP) [6] model has been developed to predict the type of self-assembled structure based on the geometry of the individual molecules. The dimensionless CPP is the ratio between the volume of the hydrophobic chain and the volume from the product of the effective headgroup area a_0 and the maximum effective length of the hydrophobic chain l_c, refer Figure 1. Molecules with a CPP $\leq$ $^1/_3$ will form spherical (normal) micelles, above this limit up to $^1/_2$ the micelles will be nonspherical (cylindrical or wormlike), and in the regime $^1/_2$ < CPP < 1, flexible bilayers (vesicles) are formed and finally at CPP $\sim$ 1, planar bilayers will dominate. Inverted structures (planar, cylindrical, and spherical ones) will be found for CPP > 1. Such molecules often precipitate out of an aqueous solution but form inverted micelles in oil [7].

The main difference between normal and inverted micelles lies in the difference between the interaction of the micellar shell and the solvent molecules. The hydrophilic headgroups of normal micelles are usually surrounded by water molecules temporarily bound by hydrogen bonds. No such specific binding effects exist between the alkyl chains of the shell of the inverted micelles and the oil molecules. The bound water in the shells of normal micelles contributes to the effective volume of the micelles as determined from the structure factor in scattering experiments (X-rays or neutrons). This effect is more pronounced for long-chain block copolymers such as pluronics with hydrophilic and highly hydrated polyethylene glycol groups. The effective volume of the micelles can be up to twice as large as the polymer volume fraction [8]. The micelles interact similar to a hard sphere system. The increase in effective volume leads to a glass transition at a polymer weight fraction of around 26%. This is remarkable as the

Figure 1



Visual representation of the packing geometries and the corresponding CPP values and their relation to the hydrophile-liphophile balance (HLB) number that is also used to designate amphiphiles that form oil-in-water (O/W) or water-in-oil (W/O) microemulsions in surfactant–water–oil mixtures. The lateral headgroup repulsive forces are located at a distance D above the interface [26]. Reprinted from Colloids and Surfaces A: Physicochemical and Engineering Aspects, J. Israelachvili, The science and applications of emulsions - an overview, 91,1-8, Copyright (1994), with permission from Elsevier. CPP, critical packing parameter.

glass transition for spheres is expected to occur at a volume fraction of 58%.

The situation is quite different for inverted micelles. There the shells can also have strong interpenetration which leads to interaction radii that are much smaller than the shell radius. The strong interpenetration leads to a slowing down of the collective diffusion as determined by dynamic light scattering (DLS) [9], while it linearly increases with concentration for nonpenetrating hard sphere systems [8].

Cylindrical micelles are usually very flexible and are therefore often called wormlike micelles. Differently to polymers they can easily break and recombine which results in specific rheological properties [10,11]. As a result of curvature effects, the end cap of wormlike micelles has a larger radius than the cylinder and therefore they appear like a match [12,13]. Wormlike micellar solutions which are stable at low temperatures are important for many applications [14]. Wormlike micelles can not only form in aqueous solution but also in polar organic solvents [15]. New quantitative theoretical approaches are able to describe the growth of wormlike nonionic micelles [16]. Many aspects of wormlike micelles including inverted or reverse ones can be found in a Soft Matter Series book [17].

Inverted or reverse wormlike micelles form in apolar media such as alkanes and cyclohexane. Highly viscoelastic reverse wormlike micellar systems can be created which even show unusual shear-thickening behavior [18]. Reverse wormlike micelles are often formed by nonionic surfactants but can also be created from ionic surfactants [19].

Cylindrical surfactant assemblies can not only grow into long wormlike micelles but they can also form branched micelles by forming Y-junctions [13]. Branched wormlike micelles and their networks have been studied intensively [11], and their rheology has been reviewed [20]. Even more complex structures such as discs and ribbon networks can be formed [21]. Branching and alignment in reverse wormlike micelles was studied with simultaneous dielectric spectroscopy and rheological small-angle neutron scattering (RheoSANS) [22]. Reverse micellar networks are also often called organogels. They can be useful for drug delivery [23].

Swollen micelles or microemulsions (see next section) can form if a second liquid phase, immiscible with the solvent, is added to micelles [1]. Spherical micelles swell up to a solubility limit and they show increasing size polydispersity. Addition of alcohols can introduce a sphere-to-rod transition. Traces of water can introduce a sphere-to-worm transition in reverse micellar systems accompanied by an increase of the viscosity of up to five orders of magnitude [24]. Water and bile salts can separately act as primers to promote the spherical to wormlike transition of lecithin reverse micelles in cyclohexane [25].

Microemulsions

Adding a second fluid, immiscible with the solvent, to a micellar solution leads to the swelling of micelles and the formation of microemulsions [27]. A microemulsion is an isotropic solution containing substantial amounts of both a strongly polar component (water) and a strongly apolar component (oil) that are stabilized thermodynamically by amphiphilic molecules [1]. Microemulsions can form without energy input because of the extremely low interfacial tension in such systems. The interfacial free energy times the area of the colloidal object is provided by the thermal energy kT.

In such complex multicomponent systems, the definition normal and inverted is usually replaced by oil-in-water (O/W) and water-in-oil (W/O) microemulsions. For the description of the geometry of the self-assembled structures, the spontaneous curvature H_0 [1] of the interfacial film is used rather than the CPP model. Positive H_0 values are defined for interfaces that bent toward oil, corresponding to CPP values < 1, and negative H_0 values for interfaces that bent toward water, where CPP > 1. Consequently, a H_0 value of zero corresponds to CPP ≈ 1. In an O/W microemulsion, oil-swollen micelles are distributed in the continuous water phase and H_0 is positive, and in W/O microemulsions, the continuous phase is the oil and micelles contain water in their core and H_0 is negative. For $H_0 \approx 0$, bicontinuous microemulsions are formed where a surfactant monolayer separates the continuous polar and nonpolar compartments.

For microemulsions, there are no limitations for the content of the three components, and their phase behavior is described by phase diagrams. An additional dimension can be added (phase prism) to describe the influence of important parameters such as temperature for nonionic surfactants or salinity for ionic surfactants or the content of an additional component.

The details of the phase prisms can be quite complicated, and it is therefore very useful to study specials cuts, for example, for nonionic surfactants, the 'fish cut' with a fixed oil/(water + oil) volume fraction Φ of 0.5 with increasing surfactant content γ as a function of temperature or the 'Shinoda cut' at a fixed value of γ for a varying Φ values. The latter shows a one-phase channel with a clear example of normal and inverted structures. On the water-rich side, one can find discrete globular to wormlike O/W microemulsions with increasing temperatures. The corresponding inverted W/O microemulsions are found on the oil-rich side with decreasing temperatures. At Φ values around 0.5, a bicontinuous microemulsion is found.

A fluid, isotropic micellar solution can transform into a highly viscous ordered liquid crystalline phase under certain conditions [28]. Such liquid crystal (LC) materials are called lyotropic if phases with long-range orientational order are induced by the addition of a solvent to amphiphilic molecules. With increasing surfactant concentration, there is a decreasing amount of water available for the hydration of the hydrophilic headgroups. This leads to a change in the interfacial curvature resulting in different LC symmetries. The most famous LC materials with distinct structure and symmetry that form upon increasing surfactant concentration are the micellar cubic, the hexagonal, the bicontinuous cubic, and the lamellar phase. Their reverse counterparts are the reverse bicontinuous cubic, the reverse hexagonal, and the reverse micellar cubic structure. Similar structural sequences can be found in block copolymer bulk phases. Maybe the most important example of lyotropic LCs is the binary system of nonionic surfactants and water which also depends strongly on temperature. Similar, but hardly temperature-dependent phase diagrams exist for ionic surfactants. Often such LC phases coexist with an excess solvent phase, a property which is important for the creation of hierarchically organized systems.

The structures of micelles, microemulsions, and LCs have been studied extensively by several different methods including transmission electron microscopy (TEM), small-angle X-ray scattering (SAXS), small-angle neutron scattering (SANS), nuclear magnetic resonance (NMR) diffusometry, and electric conductivity [29–32]. TEM methods can directly visualize the local structure in the systems, while the indirect scattering techniques SANS and SAXS are well suited to study structures and structural evolutions in situ and at high concentrations. However, they are not able to detect bicontinuity [33] like NMR diffusometry [34]. Microemulsions have a wide range of applications [27].

Kinetically stabilized systems

Vesicles

They can be considered as the simplest example of a hierarchically organized system and are built by lamellar phases, coexisting with excess solvent. When these molecules are dissolved in a solvent, they typically form multilayer aggregates of bilayers. High shear forces, for instance, from sonication or ultrafiltration, are necessary to create vesicles. If only one bilayer is involved, they are named small or large unilamellar vesicles. In case of multiple bilayers, onion-type vesicles or multilamellar vesicles can form. The size of the vesicles primarily depends on the bending elasticity of the bilayer.

Sometimes vesicles may appear ‘spontaneously’ when preparing the lipid–water system [1], but in such cases, it is unclear if shear forces are not involved during the mixing process. However, it is possible to create vesicles spontaneously by mixing two micellar solutions [35]. It has been demonstrated that vesicles do spontaneously form in extremely dilute catanionic surfactant systems if one of the components is produced by a chemical reaction [36].

Vesicles are highly interesting self-assembled structures not only as model systems for biological cell membranes but also as suitable delivery systems that allow encapsulating active agents either in their aqueous interior or in their hydrophobic bilayer [37], thereby producing delivery vehicles that are well targeted for interacting with cell membranes [38]. Advances in therapeutic applications of extracellular vesicles had been reviewed recently [39,40]. Recombinant extracellular vesicles can be used as biological reference material [41]. Strategies for the use of extracellular vesicles for the delivery of therapeutics had been reviewed recently by Sil et al. [42]. Polymer vesicles, also known as polymersomes, are finding increasing applications in the biomedical field [43].

Reverse vesicles are self-closed spherical structures in which surfactant inverted bilayers (head-to-head) separate well-defined interior and exterior apolar phases. They can be understood as counter structure of biological membranes [44]. Kunieda et al. [45] have reported on the formation of reverse vesicles in a system without adding water and have demonstrated the spontaneous formation of reverse vesicles by diluting isotropic solutions with decane and other hydrocarbons. Reverse vesicles can form under sonication from silicone surfactants in different types of silicone oil upon the addition of a certain amount of water [46]. Reverse vesicles can also form in triglycerides with some water added [47]. Vesicles and reverse vesicles can even be formed by an ionic liquid in ionic liquids [48].

Bicelles [49] (bilayer micelles) or nanodiscs can form in multicomponent systems where a second amphiphilic molecule with a low CPP forms a stabilizing rim around the bilayer fragments before they aggregate. Bicelles are interesting systems to assess the possibility and practical consequences of reconstituting integral and peripheral membrane proteins [50]. Nanoparticulate phospholipid bilayer disks (nanodiscs) can be assembled from phospholipid and a class of amphipathic helical proteins termed membrane scaffold proteins [51,52]. Similar bicelles can be formed by self-assembling peptides, and they can stabilize membrane proteins [53]. To our knowledge, no reports on reverse bicelles dissolved in nonpolar fluids have been published.

Emulsions and dispersions

A dispersion is a system in which particles of one phase are dispersed in a continuous liquid phase.

Consequently, one is calling these two phases the dispersed phase and the continuous phase. For the specific case of a two liquid phase system such as oil in water, these systems are called emulsions, and solid particles in water are dispersions.

In an emulsion system, the liquid phase to be dispersed is broken into small droplets in the continuous phase. Such droplets are not stable and coalesce within short time, eventually resulting in phase separation, unless they are stabilized by an interfacial layer of amphiphilic molecules or particles. In the latter case, one talks about Ramsden or Pickering emulsions [54]. To adsorb at an interface, particles need to be partly wetted by both phases. For a preferentially water (respectively oil) wetted particle, the contact angle θ is smaller (respectively larger) than 90°. Hence O/W (respectively W/O) emulsions are obtained for contact angles smaller (respectively larger) than 90°.

The stabilizer kinetically stabilizes the emulsion through steric or charge stabilization mechanisms. Emulsions can be of both types, O/W and W/O, and one can also create double or multiple emulsions such as W/O/W or O/W/O emulsions. For instance, in the field of food emulsions, both types of emulsions are important: O/W emulsions are found in creams and mayonnaise, while butter, margarines, and spreads are W/O emulsions. In the field of oil recovery, W/O emulsions are dominant and O/W emulsions are there referred to as reverse emulsions [55]. The names are not related to the volume fraction of the two components but to their function. Hence, an O/W emulsion consists of oil droplets dispersed in the continuous water phase and vice versa.

The volume fraction of the dispersed phase can exceed 50%. In such cases, one is talking about high internal phase ratio emulsions if the volume fraction is beyond 74% (densest packing of uniform spheres). Dispersed phase volume fractions up to about 95% were reported, leading to interesting rheological behavior with potential for applications in food science [56,57]. Emulsions have a pronounced polydispersity in the droplet sizes, depending on the production procedure. Their polydispersity can be reduced to about 10% by a fractionated crystallization procedure. Up to a volume fraction of 50%, the emulsions show a hard sphere interaction [58]. They show shear-induced crystallization at volume fractions above 49% [59]. In terms of stability, there is an important difference between O/W and W/O emulsions: O/W can be stabilized by both steric and electrostatic repulsion. For W/O emulsions, only steric forces are expected as no long-range forces are present in the nonpolar media, as the dissociation of surface groups is very unfavorable in low-polarity media [57,60]. Stable W/O emulsions can be formed by hydrophobic silica particles, and their stability against sedimentation increases with particle concentration. However, they were found to invert to an O/W emulsion at water volume fractions around 0.7 [61].

A comprehensive review on emulsions and emulsion stability in chemical and energy industries had been published recently [55].

Emulsions of self-assembled phases

Self-assembled structures such as LC phases or microemulsions can be dispersed in a solvent by energy input and stabilized by the addition of a stabilizer. However, this is only possible if the structures coexist with excess of solvent. The dispersed particles are still internally self-assembled and can therefore be summarized as internally self-assembled particles (isasomes) [62]. These isasomes can, at least in principle, be of O/W or W/O type.

The stabilizer must fulfill special conditions: it must adsorb to the isasome — solvent interface without destroying the internal self-assembled structure or should not intercalate too much into the latter. Such isasomes are a typical representative for a relatively simple hierarchically organized system: the interior of the isasomes is self-assembled but the particles are formed by a kinetic stabilization process.

Most important examples of self-assembled structures that can be dispersed into isasomes are the LC phases formed by low hydrophile-liphophile balance (HLB) amphiphilic molecules such as monoglycerides or phytantriol in water. The pure lipids form an inverted micellar L_2 phase. Upon addition of water, bicontinuous reverse cubic (V_2) phases are formed at low and ambient temperatures, while reverse hexagonal H_2 phases and fluid reverse micellar L_2 phases are found at higher temperatures. More than about 40% water, the self-assembled phase coexists with water.

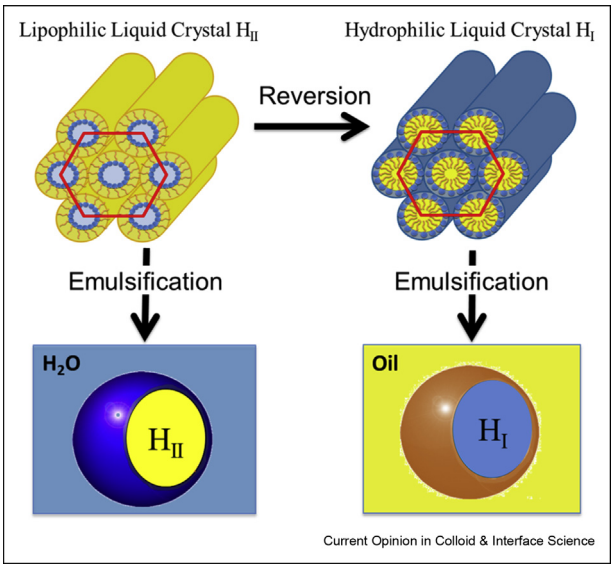
The V_2 phases can be dispersed into stable, submicron-sized particles, named 'cubosomes' [63], most often stabilized by a polyethylene oxide–polypropylene oxide–polyethylene oxide triblock copolymer with a high HLB value and a high molecular weight. Intriguingly, cubosomes could also be formed in the absence of a stabilizer with specific preparation protocols [64]. Gradients in the self-assembled structure on the surface of the stabilizer-free cubosomes with surface-bound lipid bilayers appeared to stabilize the particles for at least several weeks. The isasomes are usually in the size range of hundreds of nanometers. The transition from cubic to hexagonal to micellar can be triggered not only by temperature increase but also by addition of a third hydrophobic component (oil) [65]. When the internal structure of the dispersed particles consisted of a reverse hexagonal phase H_2, they were termed 'hexosomes', the oil-induced L_2 phase is a W/O

microemulsion and the system is referred to as emulsified microemulsion (EME) [66]. Addition of oil-like tetradecane can also lead to the formation of reverse micellar cubic phases (micellar cubosomes) [67].

Isasomes are stable over periods of months, if not years, when stored in aqueous solution. But as soon as they are mixed with other solutions with different composition, they will start to exchange material for entropic reasons [68]. The molecules of the exchanging components have to be transferred through the aqueous phase if particle fusion can be excluded. This transfer highly depends on the water solubility and is supported by free amphiphilic molecules, that is, free stabilizer micelles in the solvent [69]. Furthermore, the transfer rates may depend on the mobility of the isasomes. This can be restricted by embedding the isasomes into a hydrogel [70,71]. Arrested diffusional dynamics of the isasomes can strongly reduce the material transfer rates [72]. As the addition of free stabilizer molecules, especially above their CMC, to the system increases the transfer rates, it could be expected that a system without micelle-forming stabilizers would have much slower transfer rates. However, a Pickering isasome emulsion stabilized by hydrophobized silica particles showed transfer rates faster by a factor of about 5. The outer shell of the polymeric layer, consisting of fully hydrated polyethylene oxide (PEO) chains with a length of 100 units, may act as an effective diffusion barrier for the lipid molecules, leading to the lower transfer rates than in the Pickering emulsions [73]. Transfer or release rates can be nicely controlled by different system parameters, this makes isasome emulsions interesting candidates as reaction media and drug delivery systems [74–76]. Once the isasomes are embedded in a hydrogel, the whole system can be dried, resulting in a flexible transparent foil with embedded isasomes. During the drying process, the isasomes will also loose the internal water and so their original nanostructure [77]. This nanostructure forms again within a few minutes after wetting the dried film, a proof of the equilibrium self-assembly process. Interestingly, after further addition of water to the wetted film, the hydrogel dissolves and the free isasomes still exist having the same size as before they were introduced into the hydrogel.

A completely different type of hierarchical structure can be created with the same liquid crystalline materials. However, now it is not the LC phase which is dispersed in the continuous water phase with the help of a stabilizer but the other way around: water is dispersed in the LC phase to form a W/O emulsion. Due to the high viscosity of the oil phase one can get stable emulsions without the need of a stabilizer for reverse hexagonal and micellar cubic LC systems. Emulsions can be created with reverse bicontinuous cubic phases, however, they are not stable due to water leakage through the LC phase and microemulsions do not have the necessary high viscosity [78]. It is not possible to disperse the water directly into the LC phase due to the high viscosity of the latter. Therefore it is necessary to melt the LC phase before performing the high shear emulsification process [79] with immediate cooling afterward. Such self-stabilizing W/O emulsions based on reverse hexagonal LC phases can be created using natural oils making them an interesting, emulsifier-free alternative in skin care [80]. To our knowledge there exist no reports yet on inverted, self-stabilizing O/W emulsions based on hexagonal LC phases.

Figure 2



From hexosomes to reverse hexosomes by inverting structures: from hydrophobic, reverse hexagonal H_{II} LC phase dispersed in excess water to hydrophilic hexagonal H_I LC phase dispersed in oil [81].

It is not trivial to invert isasomes. The necessary conditions are related to those for isasomes. One has to find a hydrophilic LC phase which can take up a certain amount of oil and then phase separates into a 2-phase system of the oil-swollen LC phase coexisting with excess oil. The molecules forming the LC must have a high HLB value and a low solubility in the oil. Finally, an effective, low HLB stabilizer needs to be found for this system to create a stable emulsion of dispersed droplets of the LC phase where the stabilizer has not destroyed the LC phase (Figure 2).

It is possible to create the hexagonal hydrophilic liquid crystalline H_I phase with short-chain nonionic surfactants such as polyethylene glycol alkyl ethers [82] or with high-molecular-weight triblock copolymers of type ABA. Furthermore, one can successfully stabilize the 'reverse hexosomes' with low HLB triblock copolymers — even with commercially ones — as well as with hydrophobized, commercially available silica nanoparticles

[81]. One general problem here was the interaction of the primary surfactant with the stabilizer. The system changes in the presence of the stabilizers as if the relative concentration of the primary surfactant in the LC phase was being lowered, that is, the primary surfactant interacts with and adsorbs to the stabilizer until the stabilizer is saturated. This disturbs and may even destroy the hexagonal phase H_I. Therefore, it was necessary to increase the concentration of the primary surfactant of the system. No such problems were reported for normal hexosomes. No reports on 'reverse cubosomes' or reverse W/O EMEs have been reported until now.

Applications

Owing to their unique nanostructural features with substantial lipid—water domains and overall low viscosity, isasomes including EME, cubosomes, and hexosomes are gaining popularity as nanocarriers for the delivery of hydrophobic and amphiphilic drugs and peptide molecules [83—88]. For targeted delivery applications, the nanocarriers can be modified to respond to an external stimulus such as temperature, pH, or light for triggering the release of therapeutic molecules or enhancing the interactions with cells on demand owing to structural alterations in these nanocarriers [83,85,86,89,90].

Lipidic mesophases have recently been used for the design of nanoreactors to catalyze reactions in confined water environments [91,92].

'Swollen' lipid cubic nanostructures with lattice constants up to around 30 nm, compared with values around 10 nm for previously reported V_2 structures, were also created for the crystallization of membrane proteins with large extracellular domains through modified membrane composition [93] The lattice constant could even be extended up to 68 nm in metastable superswollen lipid bicontinuous cubic structures by combining modified lipid composition with organic solvent drying methods [94].

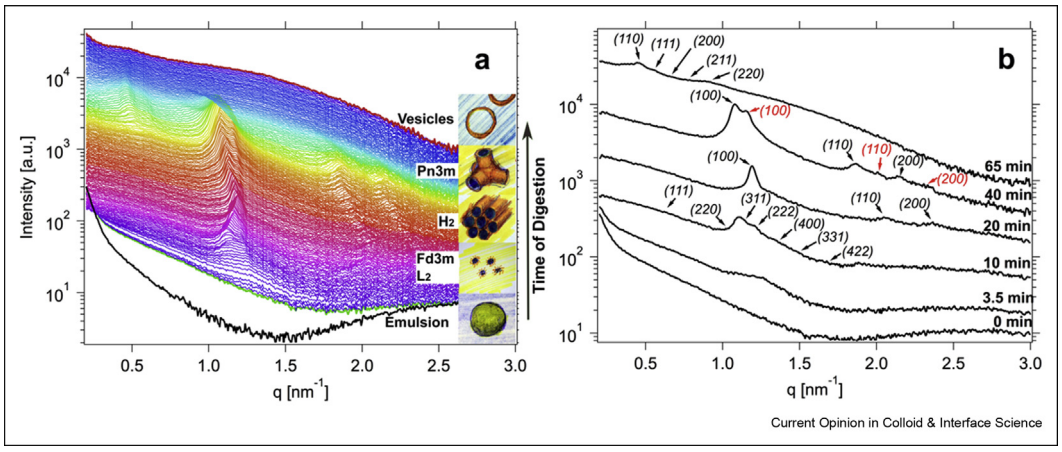
Self-assembled structures from coassembly of glycerol monooleate and oleic acid with antimicrobial peptides have recently been designed as potential alternatives to conventional antibiotics [64,85,95]. These structures can protect the peptide in the harsh biological environment and even trigger its antimicrobial activity through pH-induced phase transitions [86]. Recently, stabilizer-free cubosomes with *Pn3m*-type structure were prepared and used as precursors for antimicrobial peptide integration [64]. The resulting glyceryl monooleate (GMO) peptide coassemblies showed high antimicrobial activity against multiple bacteria strains combined with promoting activity for cell proliferation and ideal combinations for advanced materials for medical applications such as wound healing [64].

Self-assembled structures such as micelles and the more complex isasomes were discussed to play a major role in food-related materials and their digestion [2,3,96]. Bile salts on their own or together with lipids self-assemble into direct micelles that can solubilize hydrophobic molecules and facilitate their transport to the adsorptive cells of the small intestine [97]. The formation of isasomes was recently discovered during the pancreatic lipase-catalyzed digestion of model triolein-in-water emulsions, milk and triglyceride-based food products using an in vitro intestinal digestion model coupled with SAXS and cryo-TEM [3,98—100]. Transformations of the normal emulsion droplets to the L_2 phase, the *Fd3m* structure, the H_2 phase, the bicontinuous cubic *Pn3m* and *Im3m* phases, and eventually to also vesicles and normal micelles were discovered (Figure 3). The nanostructure formation inside the emulsion droplet during lipid digestion in the gastrointestinal tract may indicate a mechanism for maintenance of lipid absorption under compromised digestion conditions such as low bile salt concentrations.

Inverse self-assemblies in nonpolar medium have attracted attention for solubilization of drugs as chemical reaction platforms, as biofuel, as food material, and as solvents in biotechnology [5]. For instance, the so-called oleogels were researched to steer the physical properties of oils to control texture, viscosity, and nutrient release properties through the formation of inverse structures [101].

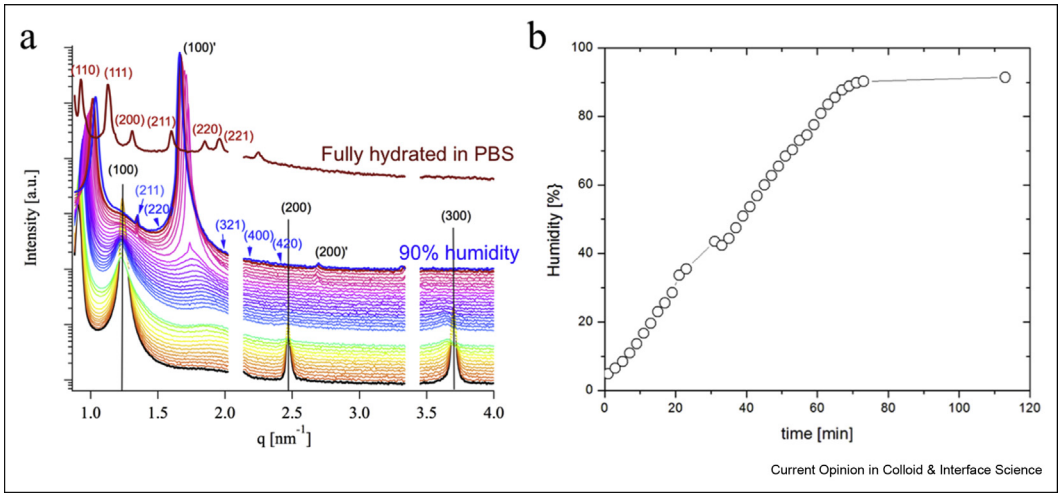
Inverse lyotropic liquid crystalline structures that coexist with excess water were recently developed into functional coatings for applications such as drug delivery [4,102,103]. Mixtures of soy phosphatidylcholine and glycerol dioleate at the silicon—aqueous interface formed inverse hexagonal (H_{II}) and micellar cubic phase (*Fd3m*) layers where the cylindrical micelles of the H_{II} structure were found to align with the interface [104]. Hydration-dependent glycerol—monooleate films were designed on silicon surfaces showing structural transformations from lamellar to inverse bicontinuous cubic structures upon hydration (Figure 4) [4]. These films offer a multidimensional surface area with confined nanosized water channels which can modify the release of components such as drugs from the surface. It may be applied to steer tissue integration or wound healing and may further protect sensitive biomolecules from degradation. In situ grazing incidence small angle X-ray scattering (GISAXS) experiments together with atomic force microscopy were performed to elucidate the mechanisms at play behind the coating formation during solvent evaporation and hydration [4]. These phase changes can be associated with distinct changes in optical and molecular diffusional properties in these materials, making them a unique platform for various applications including biosensing, nanotemplating, and drug delivery [105—107].

Figure 3



In situ small angle X-ray scattering (SAXS) during lipolysis of mayonnaise in an in vitro digestion model. **(a)** Time resolved SAXS profiles acquired during 80 min of digestion. The inset presents an artistic view of the nanostructural transitions in agreement with the SAXS data. **(b)** Representative SAXS profiles from (a) with identifiable Bragg peaks and further calculated theoretical peak positions indexed with the corresponding Miller indices for the micellar cubic *Fd3m* phase at 10 min; the H_2 phase at 20 min and 40 min (second coexisting H_2 indexed in red); and the bicontinuous cubic *Pn3m* phase at 65 min [98].

Figure 4



In situ grazing incidence small angle X-ray scattering (GISAXS) during the hydration of a glycerol monooleate film. **(a)** GISAXS patterns demonstrating the humidity induced transformations in the nanostructure of the glycerol monooleate film on silicon substrate at 28 °C between 5% and 100% humidity. The identifiable Bragg peaks and further calculated theoretical peak positions are indexed with the corresponding Miller indices for the lamellar structure in black and the *Ia3d* and *Pn3m* type cubic structures in blue and red. **(b)** The corresponding humidity values, measured directly in the GISAXS humidity cell are plotted [4].

Conclusions

Soft colloids including emulsions, microemulsions, and LC phases are found in many natural systems and industrial processes. These systems span over the full range of colloidal dimensions and interactions, where emulsions possess dimensions in the micrometer range and are kinetically stable, and microemulsions and LC phases are thermodynamically stable self-assembled structures in the nanometer range. The self-assembly of amphiphilic molecules in a solvent leads to a rich variety of nanostructures including microemulsions and liquid crystalline structures, depending on composition, temperature, and environmental conditions. If microemulsions and LCs can coexist with excess solvent, they can be dispersed in the solvent to internally hierarchically structured particles, isasomes.

In the future, a fundamental understanding of the mechanisms underlying self-assembly structure formation in the aqueous and specifically also the mostly

neglected nonaqueous counterparts can unlock key questions in fundamental biology and colloid chemistry. They have significant potential for the design of prototypic biomimetic materials for health applications and chemical or biotechnological processes.

Conflict of interest statement

Nothing declared.

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