

Vesicle Gel Formed by a Self-Organization Process

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For the first time the formation of a gel phase of densely packed unilamellar vesicles that is prepared by simple mixing of a surfactant solution and a cosurfactant (octanol) has been observed. This striking process of self-organization of a low viscous micellar phase into a vesicle phase with solidlike properties was monitored with respect to the structural and the macroscopic properties. The originally present micelles first grow in size and then form small unilamellar vesicles, which are finally monodisperse enough to form a highly ordered state. This opens a very easy way to form well-defined colloidal structures by a simple mixing process which could be of much interest for potential applications where one intends to incorporate active agents into such a vesicle phase.

Surfactants in aqueous solution can form vesicles where the size and structure of these vesicles may vary largely. Such vesicles can be unilamellar or multilamellar and their diameter may range from less than 10 nm up to several micrometers.¹ In particular, very small unilamellar vesicles have only been described in recent years^{2–5} and here even highly ordered phases of densely packed unilamellar vesicles have been observed.^{6,7}

Already this highly ordered vesicle gel is a very interesting system by itself since it constitutes a stiff gel phase with fluid surfactant alkyl chains. However, even more interesting appears to be the process of its formation described in this paper. One can start from two low viscous liquids and by a process of self-assembly a highly ordered gel phase of solidlike properties is formed. This phenomenon is particularly striking as one starts from two relatively unstructured liquids that after simple mixing self-assemble into this highly organized structure simply by diffusion processes.

The details of this process of gel formation have been investigated with respect to both the macroscopic and the microscopic changes by means of several techniques, such as electric conductivity, rheology, turbidity, small-angle neutron scattering (SANS) (performed on the instrument D22, ILL, Grenoble).⁸ For the investigations described here we chose a system composed of 182 mM Na oleate/isostearate and various amounts of added 1-octanol, i.e., a composition located centrally in the phase region of the isotropic gel.^{6,7}

The macroscopic gelation can be followed by rheological experiments. For that purpose samples were mixed and immediately afterward transferred into a rheometer (Bohlin CS-10). The rheological properties were measured in short time intervals afterward.

In Figure 1 the measured viscosity for a system containing 182 mM Na oleate or Na isostearate, respectively, and 567 mM 1-octanol is displayed as a function of time where the first data point was taken about 30 s after the mixing. Clearly evident is that the increase of viscosity occurs at least via two processes with different time scales. An initial increase of about 3 orders

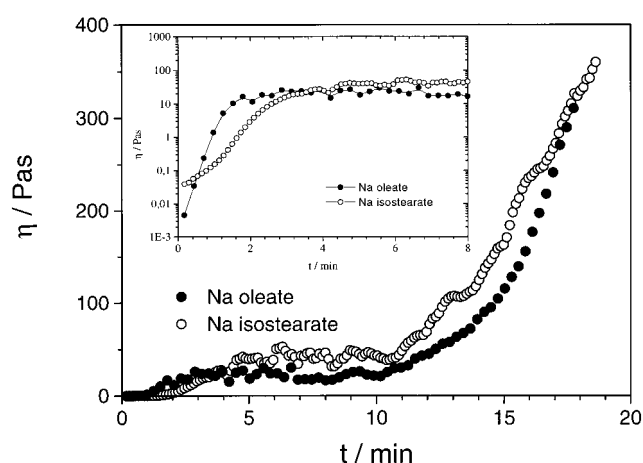


Figure 1. Viscosity η (at a shear rate of 0.22 s^{-1}) as a function of time for the gelation process of a sample of composition: 182 mM Na oleate (●) (isostearate: ○)/567 mM 1-octanol at 25°C .

of magnitude in the first minutes is followed by a long time in which the viscosity remains constant. This intermediate plateau value of $15\text{--}30 \text{ Pa s}$ is already more than a factor 1000 higher than that of the most viscous L_1 -phase of that system. This viscosity corresponds to that of equilibrated systems that contain somewhat less octanol and are made up from small vesicles.⁷

Then after about 10 min a further large increase starts until the viscosity diverges after about $18\text{--}20 \text{ min}$ due to gelification of the sample. It is interesting to note that despite the fact that the first increase was much slower for the isostearate the process of gelification occurs for both systems after a similar time.

The further process of gelification can be followed by measuring the storage modulus G' of the corresponding samples as a function of time. In Figure 2 G' (at a frequency of 10 Hz) is plotted as a function of time for samples of 182 mM Na oleate and different concentrations of 1-octanol. Evidently the gelation process depends largely on the amount of octanol present. The higher the octanol concentration the faster the process of gelation and the higher the final value of the shear modulus (it has been observed before that the shear modulus for equilibrated samples increases with increasing octanol concentration⁷). The final value

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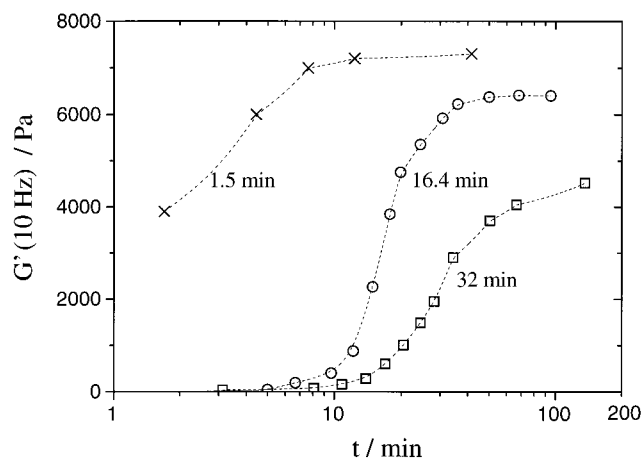


Figure 2. Storage modulus G' (measured at 10 Hz) at 25 °C measured as a function of time for samples containing 182 mM Na oleate and various amounts of added 1-octanol: (x) 567 mM; (O) 487 mM; (□) 407 mM.

of G' rises from 4700 Pa (415 mM octanol) over 6400 Pa (495 mM octanol) to 7300 Pa (567 mM octanol).

More pronounced is the effect on the kinetics of gelation. A characteristic time τ may be defined by the point where the shear modulus reaches half of its final value. This time is 32 min for 408 mM octanol, 16.5 min for 487 mM octanol, and 1.5 min for 567 mM octanol. This means that the gelation speeds up by much more than 1 order of magnitude when going from the lower phase boundary (with respect to octanol) to the upper phase boundary (cf. ref 7).

For further investigation the process of gelation was studied by means of small-angle neutron scattering (SANS), which allows us to follow the time-dependent development of the structures present. Former studies of the equilibrium systems had shown that their structure is that of densely packed unilamellar vesicles with diameters between 300 and 500 Å.⁶

The starting system was that of 182 mM Na isostearate with 567 mM octanol added, which originally became emulsified by vigorous shaking (as can be seen by the original turbidity of the samples). Such a solution of Na isostearate/oleate is known to form micellar solutions with somewhat elongated micelles.^{9,10} This means that just by allowing the octanol to diffuse from its emulsion droplets into the micellar solution one has a transformation of simple micellar aggregates to a highly ordered gel phase of unilamellar vesicles.

For the SANS experiments the components (182 mM Na isostearate solution in D₂O and the corresponding amount for 567 mM octanol) were mixed directly within the quartz cell and placed into the SANS beam immediately thereafter (i.e., after a delay of about 1–2 min the first measurements could be performed). Then the time-dependent evolution of the scattering curves was monitored for up to more than 2 days (Figure 3).

Already from a first look it is evident that the scattering pattern changes in a complex way on various time scales. For instance the scattering intensity in the low q range ($q \approx 0.01$ Å⁻¹) decreases rapidly and the time scale is identical to that observed for the initial main decrease in turbidity measurements⁸ and also to that of the initial increase of the viscosity (Table 1). The initially present broad peak around $q \approx 0.03$ Å⁻¹ rapidly develops a “bump” and afterward splits into two clearly distinct peaks. Here the one at $q \approx 0.024$ Å⁻¹ decreases in intensity with time. The intensity change in time could be fitted very well with a double exponential. The short time is again the one

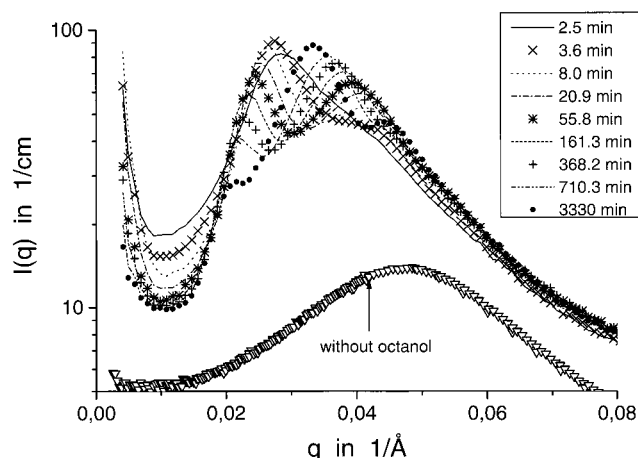


Figure 3. SANS curves for a sample of 182 mM Na isostearate/567 mM 1-octanol in D₂O at 25 °C taken at various times after mixing the sample.

associated with the gelation but the second time constant of 480 min is much longer. After times of more than 1 h one observes that a peak at $q \approx 0.04$ Å⁻¹ starts to develop that becomes much more pronounced in the course of the next hours and days. An analysis of the intensity change for this q range yields again 2 time constants that are very similar to the ones for $I(q \approx 0.024$ Å⁻¹) (Table 1).

This observation can be interpreted as follows (cf. Figure 4). The initially present micellar solution has a SANS peak around 0.048 Å⁻¹. Already in the first SANS measurement after about 2.5 min the scattering pattern has changed significantly with a much more intense peak that has moved to much lower q . Evidently, here already a large amount of the octanol has become incorporated in the micelles, which leads to a growth of the micelles and already also to the formation of vesicles (in the phase diagram vesicles start to be formed for 22 (72) mM octanol for 182 mM Na isostearate (oleate)⁸). This transformation is evidenced by the quick increase of the viscosity to the value typically observed for such vesicle systems.

Originally relatively polydisperse vesicles are formed which are responsible for the initial broad peak in the SANS curves. They become more monodisperse with time and this leads to the observed “bump” in the scattering curves that is due to the form factor of the vesicles. According to its q value they should have a radius of ≈ 120 Å, a value similar to the one observed before for the final state of such systems.^{6,7} To exhibit such a “bump” of the form factor the vesicles have to be fairly monodisperse; i.e., their polydispersity index has to be less than 0.15.

During the time that the vesicles become more monodisperse the viscosity remains roughly constant. It only increases again after about 10 min when now the vesicles are sufficiently monodisperse to form a densely packed system. Here the viscosity diverges and the sample gelifies. After this point of gelification the peak at $q \approx 0.04$ Å⁻¹ still becomes more prominent with time. Evidently, even after gelification the systems increase its degree of ordering on a time constant of about 8 h as indicated by τ_2 which appears similarly in the vanishing of the peak at $q \approx 0.024$ Å⁻¹ and the growth of the peak at $q \approx 0.04$ Å⁻¹. This ordering process can be explained in such a way that originally the vesicles form a densely packed glassy state. With increasing time they start to order more and more well, and finally form a highly ordered state. The scattering pattern observed after about 55 h looks similar to the curves observed for similarly composed samples as they have been

TABLE 1: Time Constants (min) for the Systems 182 mM Na Oleate (Isostearate)/567 mM 1-Octanol

	$\tau_1(\eta)$	$\tau_2(\eta)$	$\tau_2(0.01 \text{ \AA}^{-1})$	$\tau_2(0.024 \text{ \AA}^{-1})$	$\tau_3(0.024 \text{ \AA}^{-1})$	$\tau_2(0.04 \text{ \AA}^{-1})$	$\tau_3(0.04 \text{ \AA}^{-1})$
Na oleate	0.78	18.1					
Na isostearate	1.66	19.2	15.7	20.3	506	18.9	482

^a $\tau_1(\eta)$ is the time required for the viscosity to reach the square root of the product of initial and plateau viscosity (corresponds to half the value of the first viscosity increase in logarithmic terms) and $\tau_2(\eta)$ is the time when the viscosity diverges. The other time constants were derived from fitting the SANS intensity data with a monoexponential function for $I(q \approx 0.01 \text{ \AA}^{-1})$ and a double-exponential function to $I(q \approx 0.024 \text{ \AA}^{-1})$ and $I(q \approx 0.04 \text{ \AA}^{-1})$, that yield the time constants τ_2 and τ_3 , respectively.

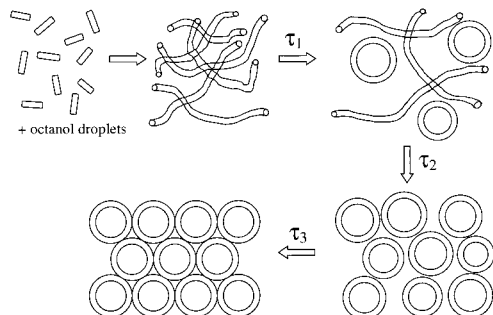


Figure 4. Schematic depiction of the structural transformations that occur after mixing together the surfactant solution and the octanol.

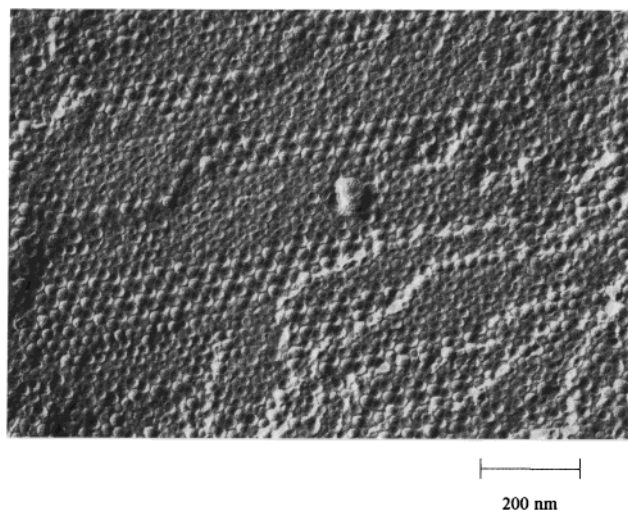


Figure 5. Freeze-fracture micrograph of a sample of 182 mM Na isostearate/567 mM 1-octanol in a mixture of H₂O/glycerol that contains 20 wt % glycerol.

prepared previously by conventional homogenization⁷ (mainly the sharpness of the peaks is somewhat more pronounced in the current case).

This highly ordered state is depicted in Figure 5 which is a freeze-fracture electron micrograph of a sample that had been prepared several days before by the same preparation method (only here instead of pure water a 20 wt % solution of glycerol in water was used). It might be mentioned here that this gel exhibits the ringing phenomenon, as it is typically encountered for cubic surfactant phases,^{11–13} and this phenomenon is already observed shortly after gelification. In Figure 5 the high degree of positional ordering of the unilamellar vesicles is very strikingly displayed and it also shows that the vesicles are clearly unilamellar. Moreover one can also observe that the vesicles are highly monodisperse. This picture looks like the ones known from textbooks for metal atoms and one can conclude that the packing of the vesicles in this final, highly ordered state should be that of a cubic phase of unilamellar vesicles. The diameter of these vesicles is 300–400 Å and in very good agreement with the value deduced from the SANS experiments.⁷

In summary one can state that in this simple experiment of just mixing together a micellar solution with a cosurfactant one obtains, starting from a low viscous emulsion, a final state of a highly ordered phase of unilamellar, monodisperse vesicles with solidlike properties. Evidently, there exists a strong driving force in this system for self-organization that transforms the disordered micellar state first into a vesicle system, where the driving force for the formation of surfactant bilayers is due to the presence of the cosurfactant octanol. However, the formation of highly curved bilayers, as present in these very small vesicles, is related to the relative mismatch between the alkyl chains of the surfactant and the cosurfactant. It has been observed by us that such a phase does not form for shorter or longer chain alcohols, but only for hexanol, heptanol, and octanol.⁷ That a certain ratio between the length of cosurfactant and surfactant should be favorable for the formation of such small vesicles has also been argued for on the basis of a molecular theory for the formation of vesicles.^{14,15}

However, it is not only the molecular composition of the amphiphilic bilayer that is responsible for the stability of the observed system but also the electrostatic conditions that prevail as has been discussed in recent theoretical and experimental work.^{4,16} That the electrostatic conditions are of significant importance is demonstrated by the fact that gel formation is only observed for not too high concentrations of added electrolyte and is also suppressed if a larger amount (40 mol %) of the anionic surfactant is replaced by a nonionic surfactant of identical chain length.⁸

However, if the proper conditions of the molecular composition and the electrostatic conditions are fulfilled, not only is one able to form very small unilamellar vesicles but also these will be monodisperse enough to form in a process of auto-organization a phase where they are ordered into a highly organized state. This means that this method of preparation of a highly structured gel phase is not only very straightforward but may be employed as a very simple and easy way to formulate gels in which active agents may be incorporated into the vesicles. This procedure is very simple since one can start from a low viscous solution of the active agent (in either the micellar phase or the cosurfactant phase). In addition, one ends up with a very monodisperse vesicle state. This state guarantees not only a very homogeneous distribution of the agent but also its presence in identical “microcontainers”, as they may be desired for a number of applications in pharmacy, cosmetics, etc.

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