# Some Rheological Properties of Nonionic Surfactant Vesicles and the Determination of Surface Hydration

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Rheological studies of dilute aqueous nonionic surfactant vesicle (niosome) dispersions formed mainly from hexadecyl diglycerol ether ($C_{16}G_2$) or sorbitan monostearate (Span 60) were performed by capillary viscometry. By variation of the ratio of $C_{16}G_2$, cholesterol, and a poly-24-oxyethylene cholesteryl ether (Solulan C24), vesicles with either polyhedral or mainly spherical structures can be formed. Polyhedral niosomes transform to spherical vesicles above a transition temperature of 45 °C, while cholesterol-rich spherical/tubular niosomes remain intact up to 80 °C. These changes in niosome morphology are reflected in their rheological properties. The relative viscosity ($\eta_{rel}$) of spherical/tubular niosome dispersions changes little with increase in temperature, while that of polyhedral niosome dispersions decreases dramatically, indicating the transformation of the vesicles to a more spherical shape. As the intrinsic viscosity, [$\eta$], of colloidal dispersions is affected not only by vesicle shape but also by surface hydration, it is possible to make estimates of hydration. The increase in viscosity with the increase in the amount of the hydrophilic Solulan C24 in the vesicle surface is a reflection of increased hydration. However, the effect of size complicates interpretation; increase in vesicle size between 270 nm and 8.8 $\mu$m reduces the viscosity of the system. Interpretation of the intrinsic viscosity data depends to a large extent on the estimation of $\phi$, the volume fraction occupied by the vesicles, because of internal hydration. Results are consistent with surface hydration in the range between 2 and 2.8 g $g^{-1}$ for niosomes containing 10% Solulan C24 at 25 °C.

## Introduction

Niosomes, unilamellar or multilamellar vesicles formed by the self-assembly of synthetic nonionic surfactants, are analogues of liposomes that have been used experimentally as drug carriers.[1−5] Published rheological studies of vesicle dispersions appear to be scarce and have concentrated either on the viscoelastic nature of the systems[6−9] or on their flow properties at high concentration.[10−11] The effect of vesicle addition on the viscosity of topical gel preparations has been studied,[12] and rheological measurements have been employed to follow the transformation of vesicles into micelles.[13] However, the rheology of dilute vesicle dispersions has not been widely investigated, and only a limited amount of work has been published.[4,14] Yet viscosity is relevant to an understanding of the flow of vesicles through capillary blood vessels, and the flow properties of some vesicle formulations might be important in quality control. There are many rheological studies of red blood cells,[15] which one may consider to be analogous to large niosomes, although the high concentration of erythrocytes in blood vessels and their distinctive shape make it unlikely that their behavior can be compared directly to that of dilute suspensions of spherical vesicles.

Einstein's viscosity eq 1[16,17] relates the relative viscosity ($\eta_{rel}$) of dilute dispersions of spherical nondeformable, noninteracting particles to the volume fraction, $\phi$, they occupy in the system:

$$\eta_{rel} = 1 + 2.5\phi \tag{1}$$

The equation is valid in situations where $\phi$ is less than 0.05. Intrinsic viscosity, [$\eta$], is defined by

$$[\eta] = \lim_{\phi \to 0}\left(\frac{\eta_{rel} - 1}{\phi}\right) = \lim_{\phi \to 0}\left(\frac{\eta_{sp}}{\phi}\right) \tag{2}$$

and is obtained by plotting $(\eta_{rel} - 1)/\phi$ (i.e., $\eta_{sp}/\phi$) vs $\phi$ and extrapolation to $\phi = 0$ (an infinitely dilute suspension). Deviation of the extrapolated value of [$\eta$] from 2.5 can be ascribed to particle asymmetry and hydration. If the particles are asymmetric, eq 1 is modified to

$$\eta_{rel} = 1 + \nu\phi \tag{3}$$

i.e.,

$$\lim_{\phi \to 0}\frac{\eta_{sp}}{\phi} = [\eta] = \nu \tag{4}$$

where $\nu$ is related to the axial ratio ($a/b$) of the particle, defined as an oblate or prolate ellipsoid.

The Einstein eq 1 was later extended by Taylor[18] to apply to deformable, spherical fluid droplets in which the fluid circulation within the globules was considered,

$$\eta_{rel} = 1 + 2.5\phi\left[\left(\eta' + \frac{2}{5}\eta_0\right)\Big/(\eta' + \eta_0)\right] \tag{5}$$

where $\eta'$ is the viscosity of the liquid in the droplets and $\eta_0$ is the viscosity of the medium. It is unlikely in multilamellar vesicles because of the internal bilayer structures that there is any such internal circulation, although in large unilamellar vesicles some fluidity and extensibility might be anticipated in shear. When the crowding effect due to the polydispersity of

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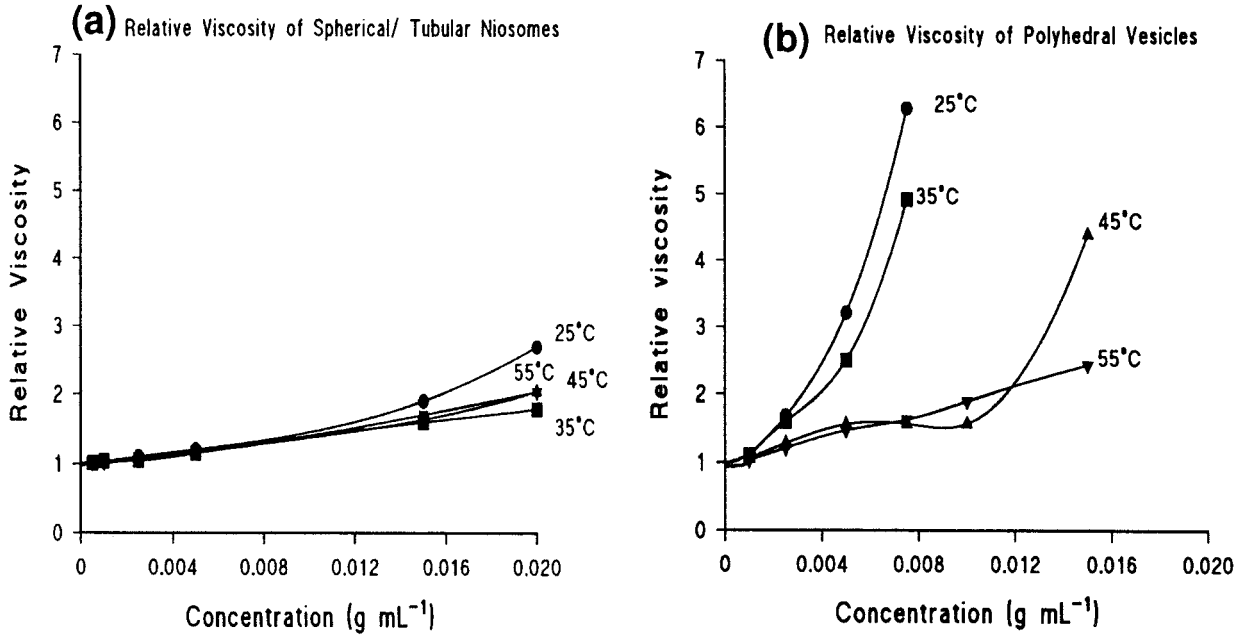


**Figure 1.** Relative viscosity of (a) spherical/tubular niosomes and (b) polyhedral niosomes of $C_{16}G_2$/cholesterol/Solulan C24 in the ratios 45:45:10 and 91:0:9 at different temperatures.

the particle diameter is considered, Mooney's[19] equation is commonly applied. This is expressed as

$$\eta_{rel} = \exp[a\phi/(1 - k\phi)] \quad (6)$$

where the symbols have the same meaning as before, $k$ being a hydrodynamic interaction coefficient related to particle size. This equation has been modified and applied successfully to many systems including emulsions and microemulsions,[20−23] latex beads,[24−25] micelles,[14] and erythrocytes.[26]

If hydrated, a particle occupies a larger volume fraction than its unhydrated counterpart. The Oncley equation[27] defines $\phi$ as $[\bar{V}_2 + W_1V_1^0]$ where $\bar{V}_2$ is the partial specific volume of the particles, $W_1$ is the solvation expressed as g solvent/g solute, and $V_1^0$ is the specific volume of the solvent so that eq 4 becomes

$$[\eta] = \nu[\bar{V}_2 + W_1V_1^0] \quad (7)$$

This equation allows the calculation of the level of hydration, $W_1$. $\nu = 2.5$ for spherical particles.

It is difficult to determine whether existing theoretical models can be applied to niosomes. Multilamellar vesicles have been treated as rigid spherical particles in previous viscometric studies;[7,8] unilamellar vesicles, which are not rigid spheres, have, however, also been treated as such.[6] The main difficulty lies in the calculation of $\phi$, which comprises not only the volume fraction of the surfactant and lipid content of the vesicles, $\phi_L$, but also the internalized water, $\phi_w$. One has no direct access to $\phi_w$. The hydrodynamic unit will, of course, include the water associated with the surface hydrophilic headgroups, which, if $\phi_w$ can be estimated, can be construed from $[\eta]$.

Various structures of niosomes can be formed by varying the molar ratio of $C_{16}G_2$ (hexadecyl diglycerol ether), cholesterol, and Solulan C24 (poly-24-oxyethylene cholesteryl ether).[28,29] Polyhedral niosomes formed in the absence of cholesterol undergo transformation into spherical structures above their phase-transition temperature, while cholesterol-rich spherical/tubular niosomes remain intact.[30] The flow properties of these two vesicular systems were studied at different temperatures. The rheological properties of sorbitan monostearate (Span 60) niosomes have also been studied as a function of mean vesicle diameter, lamellarity, and membrane composition. An attempt is made to manipulate the data into a form to which simple models such as the solid homogeneous sphere model can be applied[7,8,24,25,31] particularly to determine the hydration of the surface of the niosomes, a feature that is crucial in determining the fate of vesicles in vivo.[32, 33]

## Materials and Methods

**Materials.** Hexadecyl diglycerol ether ($C_{16}G_2$) was a gift from L'Oreal (France), and poly-24-oxyethylene cholesteryl ether (Solulan C24) was donated by Ellis & Everald, U.K. Sorbitan monostearate (Span 60) and cholesterol were obtained from Sigma, U.K. Sodium chloride and diethyl ether were supplied by BDH Laboratory Supplies (U.K.). Chloroform (HPLC grade) used for preparing the lipid/surfactant film was purchased from Rathburn Chemicals (U.K.). The water source was an ultrahigh quality reverse osmosis water purifier (Elgastat UHQPS, Elga, U.K.).

**Methods.** *1. Viscometric Studies of Polyhedral and Spherical/Tubular Niosomes.* Polyhedral and spherical/tubular niosomes were prepared by hydrating dry films of 300 $\mu$mol of $C_{16}G_2$, cholesterol, and Solulan C24 in the molar ratios 91:0:9 and 45:45:10, with 5 mL of water at 60 °C for 1 h, storing the suspensions for 24 h before experiments. Viscosity measurements were performed in an Ostwald U-tube (size M2, Phillip & Harris, U.K.) contained in a thermostated water bath (±0.1 °C). Samples were diluted with the hydrating solution to the required concentrations and left to equilibrate for 1 h. Relative viscosity ($\eta_{rel}$) was calculated by comparing efflux time ($n = 3$) with that of their hydrating solutions. Studies of micellar solutions of Solulan C24 were also performed. Changes in the morphology of 5(6)-carboxyfluorescein (CF) loaded niosomes were observed using a LINKAM system BCS 196 with temperature control fitted to a Nikon Microphot FXA light microscope.

*2. Viscometric Studies of Span 60 Niosomes.* To study the effects of vesicle size and membrane composition, dry film mixtures of 300 $\mu$mol of Span 60, cholesterol, and Solulan C24 (45:45:10 and 49.5:49.5:1) were hydrated with 5 mL of water

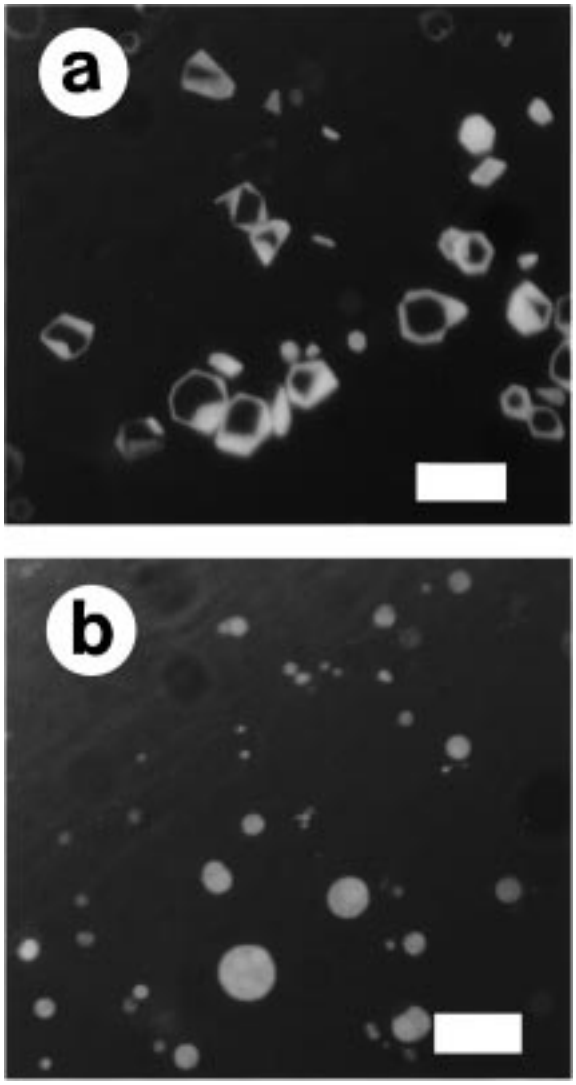


**Figure 2.** (a) Polyhedral niosomes ($C_{16}G_2$/Solulan C24, 91:9) encapsulating carboxyfluorescein show irregular faceted appearances at room temperature, and (b) at 48 °C, all polyhedral vesicles adopt spherical structures; bar = 20 $\mu$m.

at 60 °C for 1 h. All dispersions were probe-sonicated for a set period of time to obtain the required vesicle size. Particle sizing was performed using the combination of photon correlation spectroscopy (PCS, AutoSizer 2C, Malvern, U.K.) and laser diffraction methods (MasterSizer X, Malvern, U.K.). This demonstrated that all sonicated dispersions were stable over at least 1 week. Samples were also viewed by transmission electron microscopy (TEM) (Philips 201 transmission electron microscope). Rheological studies were performed using a suspended level dilution viscometer (size 2, BDH, U.K.) at 25 °C.

*3. Effects of Preparation Methods and Lamellarity.* Niosomes were prepared from 300 $\mu$mol of Span 60, cholesterol, and Solulan C24 (45:45:10) by two methods: (1) hand-shaking method (HS), where dry film was hydrated at 60 °C for 1 h and (2) the reversed-phase evaporation method (REV). Water (4 mL) was rapidly injected into the surfactant/lipid solution prepared in 10 mL of diethyl ether/chloroform (1:1), which then was bath-sonicated for 3 min. The organic solvents were removed in a vacuum evaporator at 60 °C followed by 15 min of nitrogen-flushing. The remaining dispersion was then added to 3 mL of water.

Both dispersions were then probe-sonicated for 5 min twice and then characterized by TEM and sized by PCS. Rheological studies were performed using a suspended level viscometer (size 2, BDH, U.K.) at 25 °C.

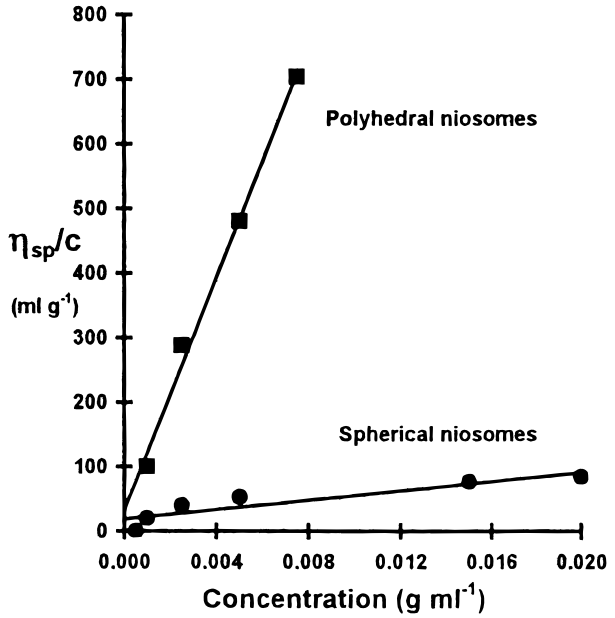


**Figure 3.** Plot of reduced specific viscosity, $(\eta_{rel} - 1)/C$, versus concentration of lipid/surfactants at 25 °C for polyhedral niosome and spherical/tubular niosome suspensions, prepared from $C_{16}G_2$/cholesterol/Solulan C24 in the ratios 91:0:9 and 45:45:10.

**TABLE 1: Intrinsic Viscosity, [$\eta$], Obtained from the Intercepts of Reduced Specific Viscosity against Concentration Plots in Water at 25 °C**

| niosome composition | mean size ($\mu$m) | [$\eta$] (mL g$^{-1}$) |
|---|---|---|
| Span 60/Cholesterol/Solulan C24 (49.5:49.5:1) | 0.278 | 9.6 |
| | 0.322 | 7.1 |
| | 8.84 | 3.5 |
| Span 60/Cholesterol/Solulan C24 (45:45:10) | 0.270 | 19.2 |
| | 8.78 | 6.5 |
| Span 60/Cholesterol/Solulan C24 (45:45:10) | | |
| sonicated from REV dispersion | 0.154 | 19.9 |
| sonicated from HS dispersion | 0.160 | 12.9 |

## Results and Discussion

**Effect of Shape Transformation on Flow Properties.** The rheological properties of spherical/tubular niosomes ($C_{16}G_2$, cholesterol, and Solulan C24, 45:45:10) (Figure 1a) change very little with increase in temperature, but as might be anticipated, the viscosity of polyhedral niosomes changes more dramatically (Figure 1b). The polyhedral niosomes have faceted structures both at room temperature and at 37 °C (Figure 2a). When the temperature is increased above the transition temperature,[30] $T_m$, of 45 °C the niosomes adopt a spherical shape (Figure 2b). As expected, suspensions of polyhedral vesicles have higher relative viscosities than their spherical counterparts. At 25 and 35 °C when the concentration of surfactants and lipids in the polyhedral systems was higher than 7.5 mg/mL, the formulation became too viscous for capillary viscometry, but above 45 °C measurements can be made. Figure 3 shows the higher reduced specific viscosities and the consequent higher intrinsic viscosity of polyhedral niosome dispersions, indicating the influence of their asymmetry, rigidity, and possibly higher hydration; polyhedral niosome bilayers have no cholesterol, it being replaced by a more hydrated surfactant.

Niosomes might be compared with rigid sphere systems, e.g., latex[24,25] or silica dispersions,[31] or systems such as microemul-

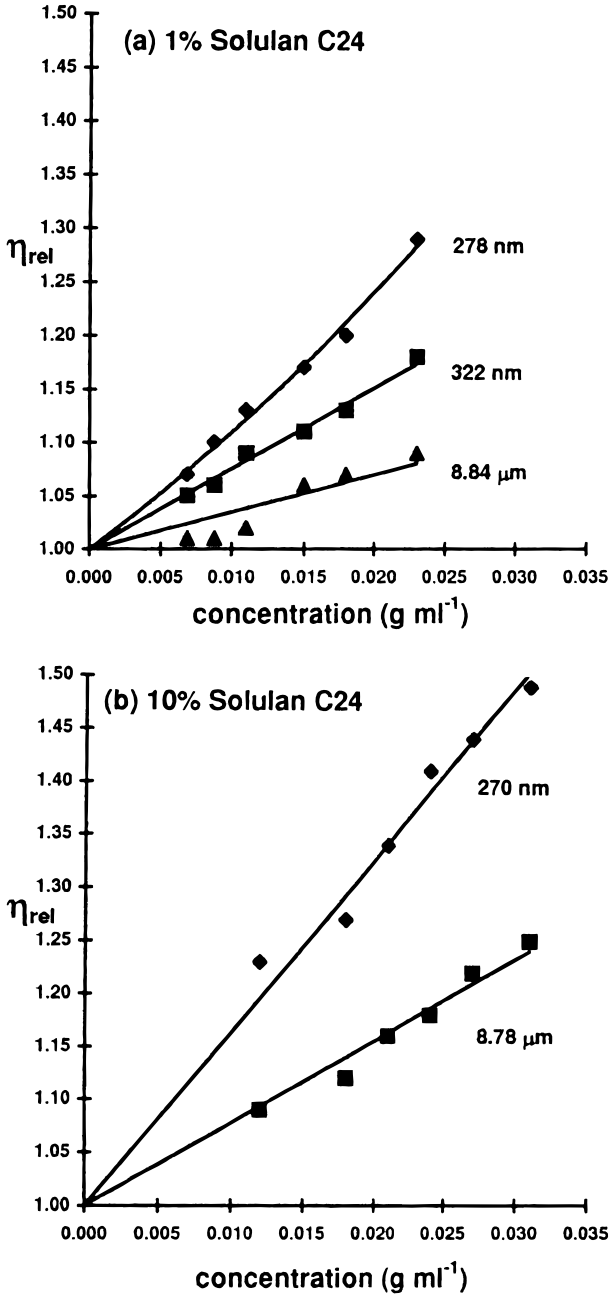


**Figure 4.** Relative viscosity of niosomes formed from (a) Span 60/cholesterol/Solulan C24 (49.5:49.5:1) and (b) Span 60/cholesterol/Solulan C24 (45:45:10) as a function of the concentration (*C*) of lipid/surfactants in water at 25 °C and of diameter.

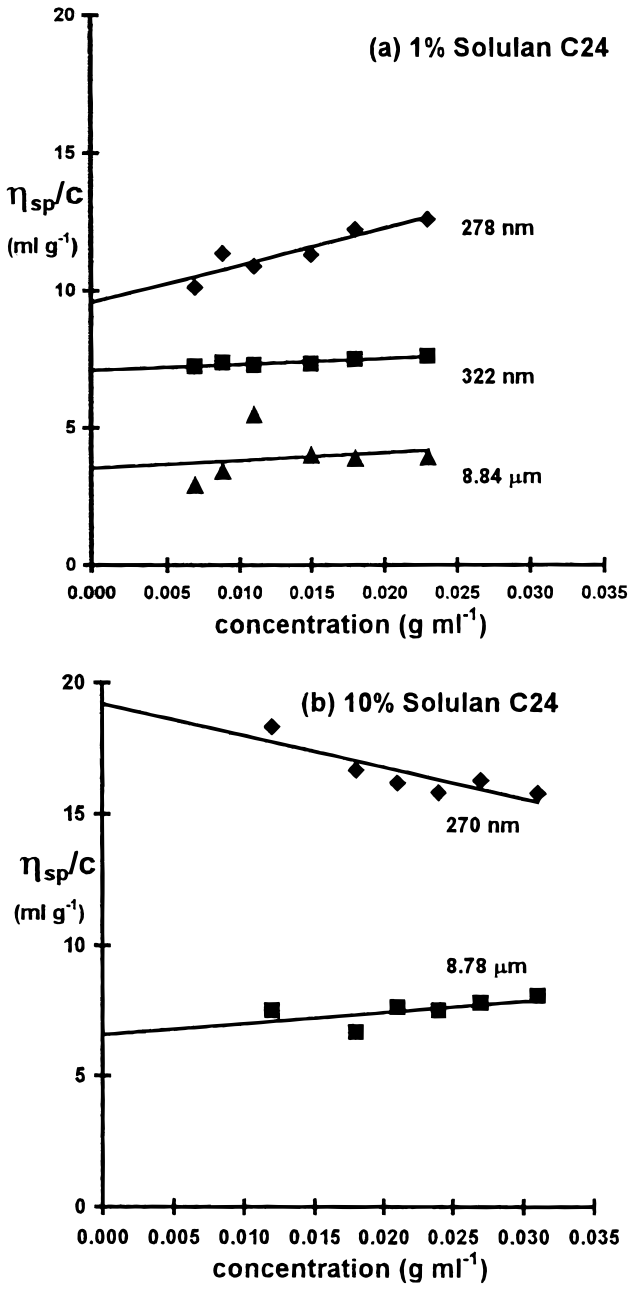


**Figure 5.** Reduced specific viscosity of niosomes formed from (a) Span 60/cholesterol/Solulan C24 (49.5:49.5:1) and (b) Span 60/cholesterol/Solulan C24 (45:45:10) as a function of the concentration (*C*) of lipid/surfactants in water at 25 °C and of diameter.

sions[20,21,23] or emulsions,[34,35] but the internal phase of unilamellar niosome dispersions must be considered to be at least partially aqueous. The true volume fraction ($\phi$) of the disperse phase may be estimated from

$$\phi = \phi_L + \phi_w \tag{8}$$

where $\phi_w$ is not measurable directly; $\phi_L$ is obtained with some accuracy from $C_L$, the concentration of lipids and surfactants used to prepared the vesicles.

**Effect of Vesicle Size and Membrane Composition.** There is a clear effect of vesicle size on relative viscosity (Figure 4) with vesicles containing 1% and 10% Solulan C24, an indication of interaction between the vesicles in suspension.

Parts a and b of Figure 5 show the plots of reduced specific viscosity versus concentration of vesicles containing 1% and 10% Solulan C24, respectively. The intrinsic viscosity of these systems, defined from these plots as

$$\lim_{C \to 0} \frac{\eta_{sp}}{C}$$

are shown in Table 1. The elevation of relative viscosity when increasing the level of Solulan C24 in the system can be seen. Polyoxyethylene chains interact avidly with water,[36] the number of bound water molecules depending on the number of oxyethylene units, particularly in micellar form.[37−39] An increased number of Solulan C24 molecules in the vesicle membranes will enhance the effective hydration of the surface of the vesicles, which otherwise is composed of sorbitan groups. Solulan C24 itself forms micelles, and the hydration of the 24 unit polyoxyethylene sheath can be calculated from the intrinsic

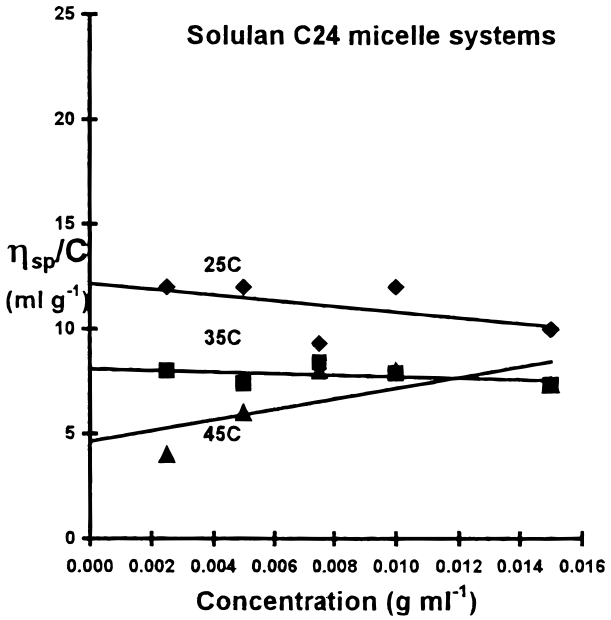


**Figure 6.** Reduced specific viscosity plots for Solulan C24 micellar solutions at different temperatures as a function of Solulan C24 concentration.

viscosity by using the modified Oncley eq 7. Assuming all densities are equal to unity, the intrinsic viscosity of micellar solutions of Solulan C24 at 25 and 35 °C is 12.2 and 8.2 mL g$^{-1}$, respectively (Figure 6), corresponding to hydration values of 3.8 g g$^{-1}$ surfactant at 25 °C and 2.3 g g$^{-1}$ surfactant at 35 °C. Elworthy[40] obtained a value of around 2 g g$^{-1}$ hydration for cetomacrogol 1000, a monocetyl ether containing an average of 22 ethylene oxide units. These values are useful in estimating the external hydration of the niosomes. For example, if the niosome surface was composed entirely of Solulan C24, the maximum hydration that would be anticipated would be around 3.8 g g$^{-1}$. It could be argued that if the vesicle size is small, they comprise virtually a condensed phase of bilayers with almost no water separating them. This would be in accord with the low values of $\eta_{sp}/C$.

**Interpreting the Intrinsic Viscosity Data.** It is not possible to determine from viscosity alone the degree of hydration of a colloidal particle unless it is spherical; vesicles are more complex because they have both internal and surface hydration. If we assume that the Einstein equation and the modified Oncley eq 7 apply to the vesicular systems under study, it should be possible to interpret $[\eta]$ in terms of the hydration of the exterior of the vesicle, provided $\phi$ is known. Figure 7 shows the model for a unilamellar vesicle with the rationale for the calculation of $\phi$ in both unilamellar and multilamellar systems. If the volume fraction of the vesicles is the volume fraction of the lipid/surfactant mixture plus the volume fraction of entrapped water, assuming for the sake of calculation that all densities are equal to unity, then we can convert reduced specific viscosity vs concentration plots into $\eta_{sp}/\phi$ vs $\phi$ for a range of assumed relationships where $\phi = f(C)$, $f$ being 1.5, 2, etc.

If the internal hydration of the vesicle is 1 g/g surfactant, $\phi \approx 2C$. Figure 8 shows the data from Figure 4a for niosomes containing 1% Solulan C24 plotted as $\phi = 2C$. The intrinsic viscosity is 4.79 mL g$^{-1}$, which suggests a hydration value of 0.92 g g$^{-1}$, but when $\phi = 2C$ for the 8.8 $\mu$m vesicles, the intrinsic viscosity calculated falls well below 2.5 mL g$^{-1}$, implying that $\phi < 2C$. If we assume $\phi = 1.5C$ (Figure 9), $[\eta] = 6.39$ mL g$^{-1}$, which, from the modified Oncley equation, implies a hydration of 1.5 g g$^{-1}$.

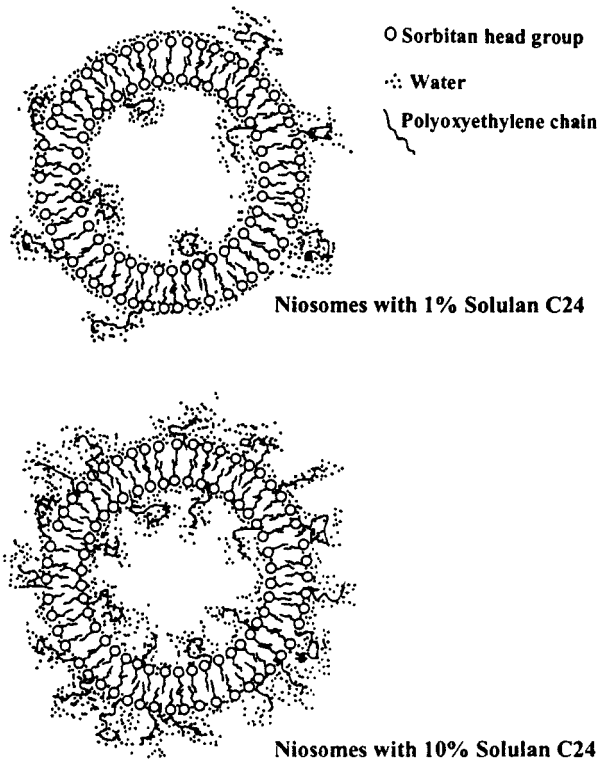


**Figure 7.** Diagrammatic representation of unilamellar niosomes containing low and high (1 and 10%) amounts of Solulan C24 with their hydration associated with the oxyethylene chains both internally and externally. The viscosity of the more hydrated form will be higher at any given value of concentration of lipids both because of the internal hydration and of the surface hydration. The lipid/surfactant bilayer occupies 20% of the total sphere volume in a unilamellar vesicle; hence, $\phi = 5C$ in this case. In a multilamellar system $\phi = C$ if there was no internal hydration. However, if we assume that the level of hydration of the sorbitan and polyoxyethylene groups are respectively 0.5 and 3.8 g g$^{-1}$, for 10% Solulan systems we can assume values of hydration around 0.8 g g$^{-1}$. In this case $\phi = 1.75C$, but when spacing and the lower density of the vesicle are allowed for, it is reasonable to assume values of $C < \phi < 2C$ (see text and Figure 8). The 1% Solulan system approximates more closely to $\phi = 1.5C$.

As stated above, if the surfaces of the vesicles are composed entirely of the long (24 unit) polyoxyethylene chains of Solulan C24, we can estimate that the hydration would be approximately 3.8 g g$^{-1}$. On the other hand, if the surface was composed largely of sorbitan groups, the figure is likely to be close to 0.5 g g$^{-1}$, the hydration value estimated from data on analogous sugars. The intrinsic viscosity data using $\phi = 2C$ to account for internal hydration of Solulan C24 containing vesicles at the level of 10 mol % suggests a surface hydration of 2.8 g g$^{-1}$ from the experimental data, which accords well with the theoretical estimates of surfaces with a mixture of polyoxyethylene and sorbitan headgroups.

Studies with the Span 60/cholesterol/Solulan C24 (45:45:10) vesicles suggest an added complication in interpretation in that viscosity is to some extent dependent on the preparation method (Table 1). The preparation method is unlikely to influence surface hydration, so differences in estimates of hydration are most probably due to the difficulty in assessing the internal hydration of the vesicles and hence the relationship of $\phi$ to $C$. In a unilamellar vesicle (~160 nm) the surfactant/lipid would occupy (from a knowledge of the dimensions of the sorbitan monostearate bilayer (~6 nm)) only 20% of the volume of the vesicle, the core being aqueous. If bilamellar, lipids occupy 38.5%; thus, $\phi$ ranges from 5$C$ down to 2.6$C$. The external hydration calculated (assuming a sphere) as if the systems were

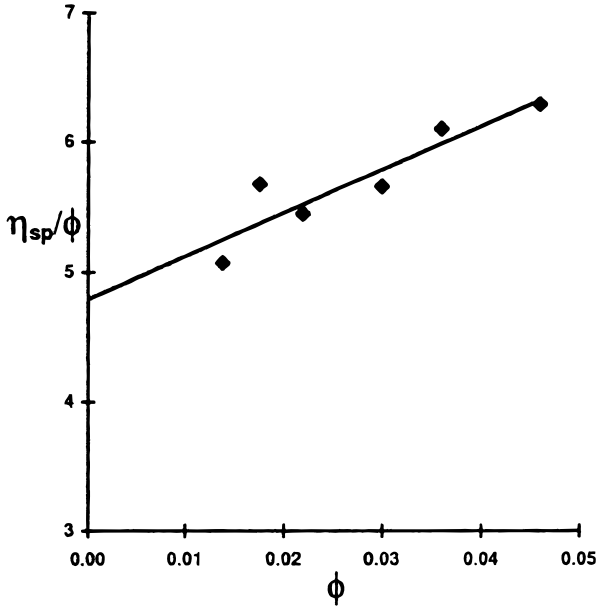


**Figure 8.** Plot of reduced specific viscosity, $\eta_{sp}/\phi$ versus $\phi$, of niosomes prepared from Span 60/cholesterol/Solulan C24 (49.5:49.5:1) with mean diameter of 278 nm using data from Figure 4a, assuming $\phi = 2C$.

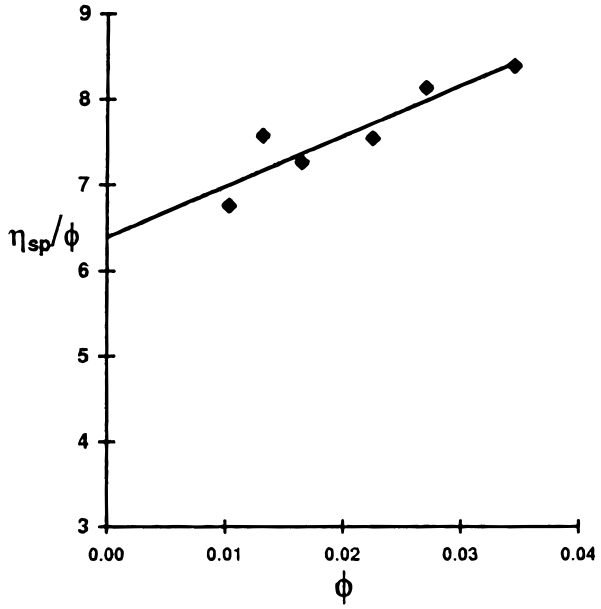


**Figure 9.** Plot of reduced specific viscosity, $\eta_{sp}/\phi$ versus $\phi$, of niosomes prepared from Span 60/cholesterol/Solulan C24 (49.5:49.5:1) with mean diameter of 278 nm using data from Figure 4a, assuming $\phi = 1.5C$.

at least bilamellar suggests again a surface hydration of ~2 g $g^{-1}$, which compares well with the experimental value of 2.8 g $g^{-1}$, discussed above.

## Conclusions

It is recognized that further work needs to be done to allow the intrinsic viscosity of niosome dispersions to be used directly to measure hydration. This aside, the relative viscosity of the systems has its own significance and the influence of formulation additives and the effect of vesicles on the rheology of blood might form the useful basis of continuing rheological studies.

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