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Viscosimetric investigation of the interaction between sodium dodecylsulfate micelles and a polymer drug carrier

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Summary

The viscosities of aqueous sodium dodecyl sulfate solutions with and without α,β-poly(*N*-hydroxyethyl)-DL-aspartamide (PHEA), at 15, 25 and 35°C are reported. The viscosities of SDS and of PHEA aqueous solutions are discussed in terms of the parameter D [$D = (\eta/\eta_0 - 1)/\phi$] describing the non-ideal behavior of SDS micelles and of PHEA macromolecules. The viscosities of SDS plus PHEA aqueous solutions, discussed in terms of the parameter F [$F = \eta_{rel}(\text{PHEA}) + \eta_{rel}(\text{SDS}) - \eta_{rel}(\text{SDS} + \text{PHEA})$], demonstrate the occurrence of interactions between SDS micelles and the PHEA macromolecule. Both D and F are scarcely influenced by temperature variation.

Introduction

α,β-Poly(*N*-hydroxyethyl)-DL-aspartamide (PHEA) is a promising drug carrier. It seems to have ideal properties, i.e., it is highly soluble in water, non-toxic, non-antigenic, non-teratogenic and biodegradable in living systems (Drobnik et al., 1979). In addition, in PHEA macromolecules, several terminal hydroxylic groups are present, which permits linking, via chemical bonds, to many drug molecules (Giammona et al., 1987, 1989, 1991).

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The potential use of PHEA and of its derivatives in the pharmacological field was the driving force for a number of investigations; their fate in the organism and their interaction with cells have been investigated (Duncan et al., 1982; Rypacek et al., 1982). The ability of PHEA to act as a targetable drug carrier was also studied by testing its pinocytic properties and, in particular, it has been shown that the incorporation of tyramine residues into its structure greatly increases cellular uptake (Duncan et al., 1985; Rypacek et al., 1985).

However, in spite of the pharmaceutical interest in this compound, few investigations on its physico-chemical properties and on its binding ability to biomembranes have previously been

carried out (Giammona et al., 1990; Castelli et al., 1991; Carlisi et al., 1992). In this recept, it must be stressed that knowledge of the binding ability of PHEA to biomembranes is of fundamental importance in order to rationalize the pharmaceutical efficiency of PHEA-drug conjugates. On the other hand, the study of binding to biomembranes is very difficult, since many uncontrollable side processes often accompany the binding, making the interpretation of the experimental data a hard task.

In order to circumvent this problem, it has been suggested to use surfactant solutions to model biomembranes. This is because these more simple systems form supramolecular aggregates sharing many of the fundamental properties of biomembranes (Fendler, 1987). It follows that the binding ability of PHEA to biomembranes can be simulated by its binding to surfactant aggregates and that this investigation enters in the field of polymer-surfactant interactions. These studies have received considerable attention for more than two decades also because of the intrinsic interest in polymer-surfactant solutions (Robb, 1981; Goddard, 1986a,b). As a consequence of polymer-surfactant interactions, many properties of polymer, surfactant and the entire solution are often strongly modified (e.g., solubility, chemical stability, rheological behavior) (Francois et al., 1985; Carlsson et al., 1986).

It has been shown that the main driving forces of the binding of the surfactant micelles to the polymeric backbone are hydrophobic and electrostatic interactions (Lewis and Robinson, 1970; Jon and Chang, 1990). Conformational changes of the polymer backbone and/or formation of a supramolecular aggregate constituted by surfactant micelles and polymer molecule have been postulated (Saito and Taniguchi, 1973; Fishman and Eirich, 1975).

In a previous calorimetric investigation (Giammona et al., 1990) on the interaction between PHEA and micelles, the observed trend of the enthalpic effect strongly suggested the binding of the micellar aggregates to the polymeric chain. In order to gain more information on this process, we have performed a viscosimetric investigation. In this paper, we report the viscosity of aqueous sodium dodecyl sulfate (SDS) solutions with and without PHEA at 15, 25 and 35°C. We have chosen the negatively charged micelles formed by SDS as biomembrane models, since in many cases the cells show the same charge on their surface (Wallach, 1969; Seymour, 1991) and there exists a wide literature on the interactions between SDS micelles with a variety of macromolecules (Jones, 1967; Murata and Arai, 1973; Paz-Andrade et al., 1978; Bloor and Wyn-Jones, 1982; Lissi and Abuin 1985; Winnik et al., 1987). In addition, since SDS and polymers are present in many pharmaceutical products, this investigation can provide information on the formulation of pharmaceutical preparations.

Materials and Methods

The preparation, purification and characterization of PHEA ($M_v = 51300$) have been described previously (Giammona et al., 1987).

SDS was a reagent-grade Sigma product and was used without further purification. Viscosities were measured with Ubbelohde micro-viscometer equipped with an AVS 440 automatic viscosity measuring unit from Schott. The micro-viscometer was chosen with a sufficiently long flow time ($t > 50$ s) in order to minimize the kinetic energy correction. The thermal stability was maintained within ± 0.01°C by a thermostatic bath. The calibration procedure was described in a previous work (D'Aprano et al., 1990).

The PHEA concentration in its aqueous solutions with and without SDS was constant (0.3952% w/w).

The densities required to convert kinematic viscosities to dynamic viscosities (η) were taken from the literature (De Lisi et al., 1984). The experimental results are listed in Table 1.

Results and Discussion

Fig. 1 shows the relative viscosities η/η_0 (η and η_0: viscosity of the solution and of the solvent, respectively) of the aqueous solutions of

TABLE 1

Viscosities (η) of SDS and SDS plus PHEA aqueous solutions as a function of the surfactant concentration at 15, 25 and 35°C

[SDS]	15°C	25°C	35°C
SDS + water			
0.00000	1.137	0.890	0.719
0.00098	1.140	0.890	0.717
0.01579	1.164	0.908	0.728
0.03200	1.212	0.948	0.763
0.05089	1.276	1.003	0.803
0.10093	1.451	1.132	0.905
0.19501	1.789	1.389	1.113
0.30781	2.273	1.768	1.425
0.45337	–	2.445	1.963
SDS + PHEA + water			
0.00000	1.269	0.988	0.797
0.00096	1.239	0.976	0.788
0.00505	1.249	0.981	0.789
0.00816	1.256	0.982	0.792
0.01009	1.276	0.988	0.795
0.01495	1.296	1.000	0.809
0.03047	1.353	1.053	0.846
0.05230	1.445	1.120	0.898
0.09876	1.613	1.255	1.005
0.20349	2.050	1.583	1.267
0.30551	2.548	1.978	1.572
0.39001	–	2.371	1.888

SDS and SDS plus PHEA as a function of SDS molonity (mol solute per kg solution) ([SDS]). In order to appreciate some features of the experimental data in the low surfactant concentration range, only those in the range $0 < [SDS] < 0.035$ are shown.

Looking at the η/η_0 vs [SDS] plots of the surfactant aqueous solutions, it can be observed that the relative viscosity begins to increase, at all temperatures, at a surfactant concentration very close to the SDS critical micelle concentration (CMC), (the CMC of SDS, practically constant in the range 15–35°C, is 8.3×10^{-3} M) (Mukerjee and Mysels, 1971). Thus, the increase in relative viscosity of SDS aqueous solutions with [SDS] can be attributed to the increase in micelle concentration.

In order to gain a better knowledge of the rheological properties of SDS micelles and PHEA macromolecules, let us consider that, for a diluite suspension of rigid spherical particles, Einstein (1956) has demonstrated that the relative viscosity is given by

$$\eta/\eta_0 = 1 + 2.5\phi \qquad (1)$$

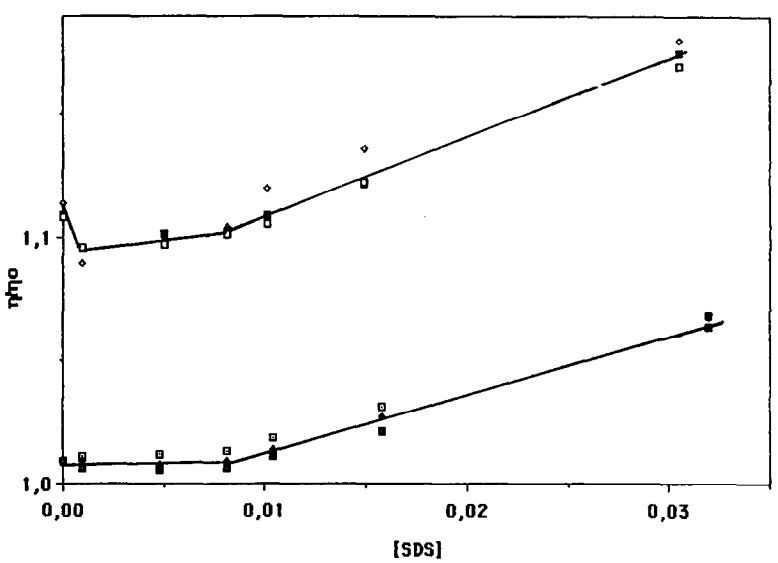

Fig. 1. Relative viscosities of SDS and SDS plus PHEA aqueous solutions as a function of the surfactant concentration: (⊡) SDS at 15°C; (♦) SDS at 25°C; (■) SDS at 35°C; (◇) SDS plus PHEA at 15°C; (■) SDS plus PHEA at 25°C; (□) SDS plus PHEA at 35°C.

where ϕ is the volume fraction of the dispersed particles.

For a real system, deviations from eqn. 1 have been attributed to (Lalanne et al., 1983; Porte et al., 1984; Okubo, 1987): (i) departures from the spherical shape; (ii) solvation of the dispersed particles (involving an effective volume fraction greater than the stoichiometric one); (iii) electroviscous effects; and (iv) dynamical properties of the dispersed particles (i.e., the particle shape fluctuation influences the rate of momentum transfer near the particle involving an increase in the viscosity of the medium).

Since SDS and PHEA form supramolecular particles in their aqueous solutions, it seems reasonable to assume the quantity D, defined as

$$D = (\eta/\eta_0 - 1)/\phi \qquad (2)$$

provides a measure of the ideality (or not) of these particles (D'Aprano et al., 1992).

For the PHEA aqueous solutions, taking into account that the partial specific volume of PHEA is 0.677 cm^3/g (Antoni et al., 1974), we have calculated the following values of D at 15, 25 and 35°C: 19.9, 18.9 and 18.8, respectively. These high D values reflect the hydration of PHEA and its dynamical properties. This is in agreement with the finding that PHEA in aqueous solution is a strongly hydrated random coil (Antoni et al., 1974).

The ϕ values of SDS solutions, evaluated according to the equation

$$\phi = ([\mathrm{SDS}] - \mathrm{CMC})dV_{\mathrm{SDS}} \qquad (3)$$

where d denotes the density of the solution and V_{SDS} is the apparent molar volume of the micellized surfactant (De Lisi et al., 1984), allowed us to calculate the D values of the SDS micelles. In Fig. 2, plots of this quantity as a function of [SDS] are reported.

As can be seen, the D values are greater than 2.5 even at very low micellar concentration. Thus, we can exclude that these large values are due to intermicellar interactions. On the other hand, if we attribute all the observed effect to solvation of the micelles, it follows that the effective volume fraction of the solvated micelles is nearly 4-times ϕ. This result seems unreasonable and other contributions may be invoked. We believe that a significant contribution can derive from the dynamical properties of the micelles. In Fig. 2, an increase in D can also be noted with increasing surfactant concentration at [SDS] > 0.2. This can be attributed to the well known sphere-to-rod transition of SDS micelles occurring in the same concentration range (Roux-Desgranges et al.,

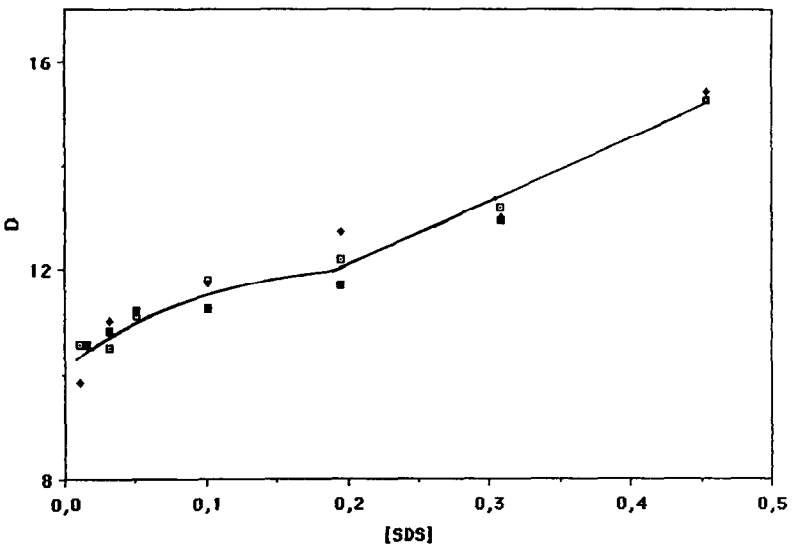

Fig. 2. D parameter (see text) as a function of surfactant concentration: (⊡) 15°C; (◆) 25°C; (■) 35°C.

1982, 1985). This hypothesis is also consistent with the idea that the D parameter of cylindrical micelles should be dependent upon the surfactant concentration because the axial ratio of rod-like micelles increases significantly with increasing concentration (Nagarajan, 1982). Finally, the weak dependence of D upon temperature can be explained in terms of compensation of different effects (see points i–iv).

Let us now consider the viscosimetric behavior of PHEA plus SDS solutions. As can be seen in Fig. 1, the initial addition of surfactant to the PHEA aqueous solution lowers the relative viscosity and this effect is scarcely dependent upon temperature. In addition, it can be also noted that below the CMC (i.e., when the surfactant is in the monomeric state), the relative viscosity is not constant.

We know from a previous calorimetric investigation (Giammona et al., 1990) that in the range $0 < [SDS] < 0.005$, a very low enthalpic effect is observed. Therefore, the observed lowering of the relative viscosity may be explained in terms of nearly athermal process. According to Cohen and Priel (1990), it can be attributed to the screening of long-range electrostatic interactions between the polymeric molecules due to the ions of the surfactant (Jon and Chang, 1990).

In Fig. 1, it can be also noted that at $[SDS] > 0.01$ (i.e., when the SDS micelles are present in the solutions), the relative viscosity increases with increasing surfactant concentration. However, the absence of net intersection points in the η/η_0 vs [SDS] plots does not allow us to determine the CMC of SDS in the presence of PHEA.

Taking into account that, if no interaction between SDS and the polymer occurs, it can be expected that (Lewis and Robinson, 1970)

$$\eta(\text{SDS} + \text{PHEA}) = \eta(\text{PHEA}) + \eta(\text{SDS}) - \eta(\text{water}) \quad (4)$$

and hence

$$\eta_{rel}(\text{PHEA}) + \eta_{rel}(\text{SDS}) - \eta_{rel}(\text{SDS} + \text{PHEA}) = 1 \quad (5)$$

According to Lewis and Robinson (1970), in order to demonstrate PHEA-SDS interactions, we

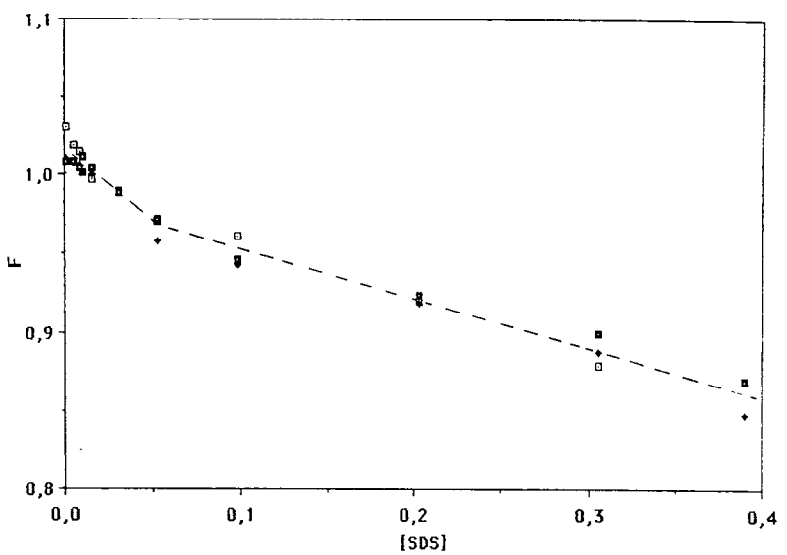

Fig. 3. F parameter (see text) as a function of surfactant concentration: (⊡) 15°C; (♦) 25°C; (■) 35°C (the dashed line is given a guide for the eye).

can assume that the quantity

$$F = \eta_{rel}(PHEA) + \eta_{rel}(SDS) - \eta_{rel}(SDS + PHEA) \quad (6)$$

is a measure of the interactions (or not) between SDS and PHEA. In Fig. 3, plots of F as a function of [SDS] are shown.

It can be observed that, with increasing [SDS], F shows a marked deviation from the ideal behavior ($F = 1$) demonstrating the occurrence of PHEA-SDS interaction.

At surfactant concentrations lower than CMC, the effect can be ascribed to the screening of the interactions between polymeric molecules due to ions of the surfactant.

At surfactant concentrations greater than the CMC, according to a previous investigation (Giammona et al., 1990), this interaction can be retionalized in terms of binding of micelles to the polymeric backbone of PHEA. In fact, as a consequence of intermicellar repulsion, the progressive binding of the negatively charged SDS micelles to PHEA will expand progressively the polymeric chain (Fishman and Eirich, 1975), involving a decrease in F. The observed binding ability of PHEA with SDS micelles allows us to infer that a similar binding of PHEA to biomembranes can be expected. Finally, the weak dependence of F upon the temperature can be taken as an indication that the stability of the PHEA-SDS complex is only slightly affected by this parameter in the investigated temperature range.

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