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Solubilization of Indomethacin by Polysorbate 80 in Mixed Water-Sorbitol Solvents

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Abstract—The effect of indomethacin on the micellar properties of the non-ionic surfactant, polysorbate 80, in water-sorbitol mixtures containing up to 25% w/v sorbitol has been investigated by light scattering, photon correlation spectroscopy and viscometric techniques. The molecular weight of polysorbate 80 micelles containing solubilized indomethacin increased linearly with increase of sorbitol concentration. Solubilization of indomethacin resulted in an increase of micellar weight due not only to the incorporation of solubilizate but also to an increase in the number of polysorbate molecules per micelle. The micelles in all systems were most satisfactorily represented as oblate ellipsoids, the asymmetry and hydration of which increased with increase of sorbitol concentration. Indomethacin solubilization caused a restructuring of the micelle to produce a more symmetrical micelle of increased hydration.

The solubilization of water-insoluble drugs by non-ionic surfactants may be used not only as a means of improving solubility in formulations for oral use (Attwood & Florence 1983) but may also have the advantage of protection of the drug against hydrolysis. The solubilizing capacity of polysorbate 80 for indomethacin has been previously studied by Kim & Choe (1984). Krasowska (1976, 1978) has reported on the solubilization of a series of anti-inflammatory compounds including indomethacin in non-ionic surfactant solutions and has demonstrated a decrease in the first-order rate constant for hydrolysis of indomethacin with increase of surfactant concentration in a homologous series of polysorbates (Krasowska 1979).

The addition of sorbitol as a sweetening agent to oral formulations containing solubilized drugs may be expected to affect the properties of the micelles of these systems. It has been shown, for example, that the presence of the dihydric alcohol, glycerol, causes a reduction of the micellar size of the polyoxyethylated non-ionic surfactant, dodecyl octaethylene glycol monoether ($C_{12}E_8$) (Cantu et al 1987). In this study we report the influence of indomethacin on the micellar properties of polysorbate 80 in aqueous solution and in solutions containing up to 25% w/v sorbitol. A combination of light scattering, photon correlation and viscometric techniques has been employed to determine changes in micellar size, shape and hydration with changes in indomethacin and sorbitol content of the solubilized systems.

Materials and Methods

Materials

Polysorbate 80 (polyoxyethylene 20 sorbitan mono-oleate) was supplied by Sigma and used as received. A nominal molecular weight of 1309·7 was assumed for the purpose of calculation, based on the molecular formula $C_{64}H_{124}O_{26}$. Indomethacin and sorbitol (Sigma) were used as received.

Methods

Light scattering and photon correlation measurements. Measurements were made at 37° ± 0·1°C using a Malvern 7027 digital autocorrelator equipped with a 3W Argon ion laser (Coherent Innova 90) operating at 488 nm. Photon correlation spectroscopy (PCS) measurements were made on the single clipped homodyne mode using 60 linearly spaced channels with a far point delay of 1024 sample times. Calibration of the instrument for total intensity light scattering measurements was with a dust-free sample of benzene (Analar). All measurements were at 90° to the incident beam, there being no significant dissymmetry of the scattered light. All solutions for PCS and light scattering were repeatedly filtered through 0·1 μm filters until dust-free. The refractive index measurements were made using an Abbe 60 precision refractometer (Bellingham and Stanley Ltd) and corrected to 488 nm.

Measurements of partial specific volume. Density measurements were carried out at 37° ± 0·01°C using a Paar DMA60 digital density meter. The partial specific volume, $\bar{v}$, of the micelles was calculated from

$$d_s = d + (1 + \bar{v}\, d)\, C \qquad (1)$$

where d_s and d are the densities of solution and solvent, respectively and C is the total solute concentration.

Viscosity measurements. A suspended level capillary viscometer with a solvent flow time of approximately 200 s was used at 37° ± 0·01°C.

Cloud point determination. The cloud point (lower consolute temperature) was determined by heating the solutions in glass vials in a water bath at a constant rate and observing visually for the onset of turbidity. Each value was a mean of four readings with a precision of approximately ± 1°C.

Preparation of solubilized systems. Solutions were prepared by warming together the required amounts of indomethacin and polysorbate 80 at 40°C before adding sufficient warm solvent to produce the required total concentration. All solutions were allowed to equilibrate at 37°C (24 h) before measurements were made.

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Results and Discussion

Cloud point studies

The cloud point (lower consolute temperature) was determined as a function of solution concentration for polysorbate 80 micelles containing an indomethacin/polysorbate molar ratio of 0·30 in water and in 25% sorbitol. In both cases concentration had an insignifiant effect on cloud point ($< 2°C$) over the concentration range 0·2 to 2% total solute. Below 0·2% the cloud point increased markedly with concentration decrease.

The influence of indomethacin on the cloud point was determined for 2% polysorbate 80 solutions in water and in 25% sorbitol. Systems with an indomethacin/polysorbate molar ratio of 0·30 had cloud points of between 4 and 6°C lower than the corresponding indomethacin-free solutions. The effect of sorbitol on the cloud point was more pronounced. The cloud point of 2% polysorbate 80 solution decreased linearly with increase of sorbitol concentration from 83°C in water to 64°C in 25% sorbitol. Similar decreases were noted in systems containing solubilized indomethacin. These results are in agreement with those of Zatz & Lue (1987) who reported cloud point depressions of similar magnitude for polysorbate 80 by sorbitol both in the presence and absence of solubilized methylparaben.

From these preliminary investigations it is clear that the temperature of 37°C selected for physicochemical measurement is sufficiently lower than the cloud point to avoid significant influence of non-ideality effects arising from proximity to the phase boundary (Cantu et al 1987).

Effect of indomethacin and sorbitol on micellar size

Fig. 1 shows the total intensity light scattering data expressed as the ratio, S_{90}, of the intensity of light scattered from the solution to that from benzene, against total solute concentration, C. The concentration range over which measurement was conducted was restricted to that of the linear portion of the cloud point curve to avoid non-ideality effects.

The molecular weight of the micelles, M, was calculated from

$$\frac{KC}{\Delta R_{90}} = \frac{1}{M} + 2BC \qquad (2)$$

where K is the optical constant, ΔR_{90} is the Rayleigh ratio of the solution in excess of that from the solvent and B is an interaction coefficient. It should be noted that in all the physicochemical techniques, measurements were made relative to the solvent rather than to a solution at the critical micelle concentration (CMC) since this was considered sufficiently low (polysorbate 80 CMC = 0·0014 g dL^{-1}, Wan & Lee 1974) to be neglected.

Table 1 shows an increase in the micellar weight with increase in sorbitol concentration; this effect becoming more pronounced with increase in the indomethacin/polysorbate molar ratio. These findings are in contrast to the decrease in micellar weight following the addition of the dihydric alcohol, glycerol, to the non-ionic surfactant $C_{12}E_8$ (Cantu et al 1987). It should however be noted that sorbitol and glycerol differ in their effects on the CMC of non-ionic surfactants. Ueda et al (1979, 1980) have reported that sorbitol caused a CMC decrease of the commercial non-ionic surfactants, Emulgen 913, 931 and 985 (general formula $C_9H_{19}-C_6H_4-O-(CH_2-CH_2-O)_n H$ with n = 13, 31, and 85, respectively) in contrast to the CMC increasing effect of glycerol noted by these authors and also by Cantu et al (1987) for the $C_{12}E_8$ system. An increase in micellar weight following sorbitol addition would be compatible with the CMC decreasing effect of this alcohol suggesting a greater solvophobic effect in sorbitol than in aqueous solution.

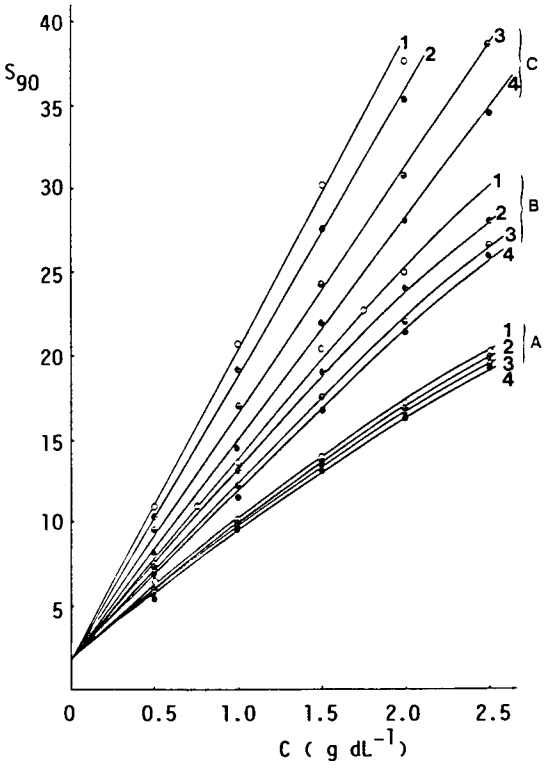

FIG. 1. Variation of light scattering ratio, S_{90}, with total solute concentration, C, for solubilized systems of polysorbate 80 in water/sorbitol solvents containing A, no indomethacin; B, 0·15 mol indomethacin/mol polysorbate 80; C, 0·30 mol indomethacin/mol polysorbate 80 with sorbitol concentrations of (4) 0; (3) 5; (2) 15; (1) 25% w/v.

Table 1. The influence of indomethacin on the micellar properties of polysorbate 80 in water/sorbitol solvents.

Mol indomethacin per mol polysorbate	Sorbitol conc (g dL^{-1})	M ($\times 10^{-5}$)	D_o (m^2s^{-1} $\times 10^{11}$)	$[\eta]$	Axial* ratio	δ $gH_2O\,g^{-1}$ solute
0	0	0·53	7·0	3·7	3·4	0·10
	5	0·55	5·7	4·3	4·0	0·14
	15	0·61	3·6	5·5	5·5	0·19
	25	0·63	2·5	6·3	6·2	0·26
0·15	0	0·74	6·8	3·8	2·5	0·32
	5	0·79	5·3	4·9	3·0	0·52
	15	0·88	3·3	6·3	4·3	0·58
	25	0·98	2·1	7·8	5·5	0·65
0·30	0	0·92	6·0	4·5	2·5	0·54
	5	1·01	4·7	5·4	3·0	0·68
	15	1·22	2·9	7·3	4·0	0·88
	25	1·43	1·9	8·6	4·6	1·03

* Calculated assuming oblate ellipsoid.

Table 1 shows that solubilization of indomethacin at constant sorbitol concentration also resulted in increases in micellar weight as might be expected. It is instructive to consider whether the observed increase in micellar weight is attributable solely to the incorporation of the solubilizate within the micelle. In view of the very low aqueous solubility of indomethacin it is reasonable for the purpose of calculation to assume that this solute resides entirely within the micellar phase. Consequently if the ratio indomethacin/polysorbate 80 within the micelle is identical to that of the system as a whole, the mean composition of the micelles may be readily determined. In Fig. 2 the number of molecules of solubilizate and of polysorbate 80 in the micelle is plotted as a function of the mole fraction of indomethacin in the system. This Figure shows that the micellar growth following the solubilization of indomethacin is attributable not only to the presence of the solubilizate molecules but also to an increased number of polysorbate molecules per micelle. A similar effect was noted following the solubilization of water-insoluble solutes in cetomacrogol micelles (Attwood et al 1971) and suggests a restructuring of the micelle to accommodate the solubilizate molecules.

Effect of indomethacin and sorbitol on micellar shape and hydration

Apparent diffusion coefficients, as determined by photon correlation spectroscopy, were linear functions of the total solute concentration. In view of the high aggregation numbers of the micelles in these systems, it cannot be assumed that these micelles are spherical. Consequently, the limiting diffusion coefficient at infinite dilution, D_o, has been related to the hydrated dimensions of the micelle by Perrin's relations (Zero & Pecora 1985) for ellipsoids,

$$D_o = \frac{kT}{6\pi\eta a} G(\rho) \quad (3)$$

where k is the Boltzmann constant, T the absolute temperature, and η the solvent viscosity. The shape factor $G(\rho)$ is related to the axial ratio ($\rho = b/a$) where a = length of major semi axis and b = length of minor semi axis. For prolate (rod like) ellipsoids,

$$G(\rho) = (1-\rho^2)^{-\frac{1}{2}} \ln \left[\frac{1+(1-\rho^2)^{\frac{1}{2}}}{\rho}\right] \quad \rho < 1 \quad (4)$$

and for oblate (disklike) ellipsoids,

$$G(\rho) = (\rho^2-1)^{-\frac{1}{2}} \arctan\left[(\rho^2-1)^{\frac{1}{2}}\right] \quad \rho > 1 \quad (5)$$

The use of equation 3 in the determination of micellar dimensions necessitates the choice of the type of ellipsoid and an estimate of the axial ratio.

The intrinsic viscosity $[\eta]$ was derived by extrapolation of plots of reduced viscosity η_{sp}/C against C (Fig. 3) where the reduced specific viscosity is given by

$$\eta_{sp}/C = \frac{\eta-\eta_o}{\eta_o C} = \frac{(t-t_o)}{t_o C} + \left[\frac{1}{\rho_o} - \bar{v}\right]\frac{t}{t_o} \quad (6)$$

t and t_o are the flow times for a solution of weight concentration C and for the solvent, respectively. ρ_o is the density of the solvent and $\bar{v}$ the partial specific volume of the

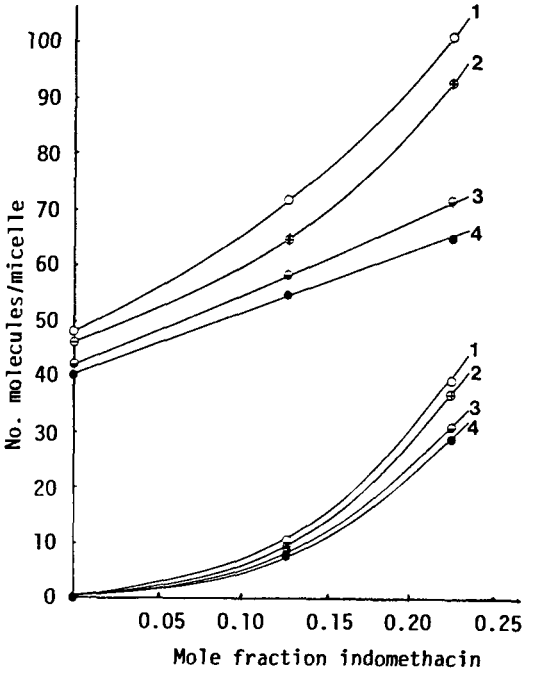

FIG. 2. The number of molecules per micelle of polysorbate 80 (upper curves) and indomethacin (lower curves) as a function of the mole fraction of indomethacin in solubilized systems with sorbitol concentrations of (4) 0; (3) 5; (2) 15 and (1) 25% w/v.

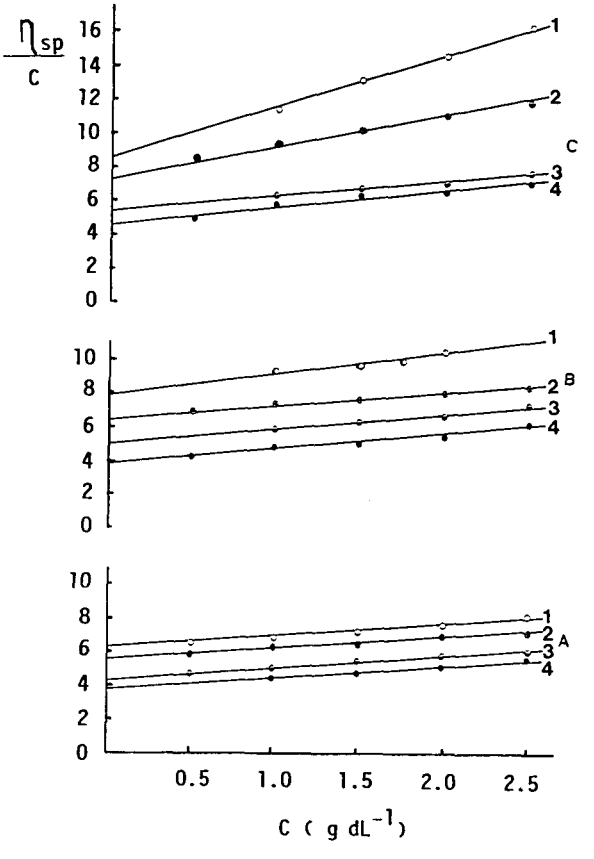

FIG. 3. Variation of reduced viscosity with total solute concentration C for solubilized systems of polysorbate 80 in water/sorbitol solvents containing A, no indomethacin; B, 0·15 mol indomethacin/mol polysorbate 80; C, 0·30 mol indomethacin/mol polysorbate 80 with sorbitol concentrations of (4) 0; (3) 5; (2) 15; (1) 25% w/v.

micelles. The intrinsic viscosity is determined both by the axial ratio and the micellar hydration according to

$$[\eta] = \nu\,(\bar{v} + \delta V_1^{\circ}) \qquad (7)$$

where δ is the hydration expressed as g H_2O per g of total solute and V_1° is the specific volume of pure solvent. The parameter ν has been related to the axial ratio of prolate and oblate ellipsoids (Mehl et al 1940). It is thus necessary to fix either axial ratio or hydration in order to further describe the micelle. Since PCS measures the hydrated micellar characteristics and total intensity light scattering measures the anhydrous micellar weight it is, in principle, possible to calculate the extent of hydration by comparison of the hydrated and anhydrous volumes derived from data from these two techniques. Such a comparison however is strictly only valid in systems in which the micelles are monosized since the micellar weight from light scattering is a weight average value whilst the diffusion coefficient from PCS is Z-average. The anhydrous micellar volume V_a, is related to the micellar weight by

$$V_a = \frac{M}{N_A}\ \bar{v} \qquad (8)$$

where N_A is the Avogadro constant. The hydrated micellar volume, V_h, may be derived for each ellipsoidal model and a selected axial ratio using equations 3–5 and the relevant equations for the volume of the ellipsoid ($V_h = \frac{4}{3}\pi\ a\ b^2$ for prolate, $V_h = \frac{4}{3}\pi\ a^2\ b$ for oblate). The volume of hydrating water calculated from the difference $V_h - V_a$ and converted to weight of water per unit weight of total solute may be compared with the value of δ calculated from the intrinsic viscosity for the same axial ratio. Iteration of the axial ratio should then permit the determination of the micellar dimensions.

Preliminary calculations showed that it was not possible to achieve any correlation of data using the model of a prolate ellipsoid. It is obvious that the asymmetry required to accommodate a given core volume must be greater for a prolate than an oblate ellipsoid with the result that the component of $[\eta]$ due to hydration becomes too small to allow any agreement with the $V_h - V_a$ value. For example in the polysorbate 80/H_2O system, calculations assuming $\rho = 1$ (sphere) lead to δ values of 4 g H_2O per g of polysorbate from the difference $V_h - V_a$ and only 0·58 g H_2O per g of polysorbate from the $[\eta]$ value. An increase of asymmetry leads to an increasing divergence between these hydration values. It was however, possible to correlate exactly the values of δ using an oblate model. Table 1 gives axial ratios and hydration values required for such correlations. Other workers have also concluded that an oblate rather than prolate model gave a better description of the micelles of non-ionic systems. An oblate model was shown by Robson & Dennis (1977) to give a good representation of experimental data for the micelles of the commercial alkylphenyl polyoxyethylene non-ionic, Triton X-100; this model was also found to be consistent with the small angle X ray curves for this surfactant (Paradies 1980). A disklike shape was found to be most appropriate to describe the micellar shape of $C_{12}E_8$ and the commercial non-ionic, Lubrol WX ($C_{17}E_{16\cdot4}$) (Tanford et al 1977).

It is stressed that the values of axial ratio and hydration of Table 1 should be treated with caution in view of the probable range of micellar sizes in these systems. This table does, however, show a clear tendency for an increase of asymmetry and hydration with increase of sorbitol in both solubilized and solubilizate-free systems. The results also suggest that the solubilization of indomethacin in systems of fixed sorbitol content causes a restructuring of the micelle producing a more symmetrical micelle with greater hydration.

Acknowledgement

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