International Journal of Pharmaceutics, 52 (1989) 165–171
Elsevier

IJP 01760

A light scattering study on oil-in-water microemulsions

D. Attwood [1] and G. Ktistis [2]

[1] *Department of Pharmacy, University of Manchester, Manchester (U.K.) and* [2] *Pharmaceutical Technology, Department of Pharmacy, Aristotelian University of Thessaloniki, Thessaloniki (Greece)*

(Received 2 November 1988)
(Accepted 21 November 1988)

Key words: Microemulsion; Light scattering

Summary

Time-average light scattering techniques have been used to determine the droplet size in oil-in-water microemulsions formed from isopropyl myristate, polysorbate 60, sorbitol and water. Data have been analysed using a procedure based on the use of a hard sphere model for interparticle interaction. Phase studies have indicated an optimum polysorbate : sorbitol mass ratio for microemulsion formation of 1 : 2. Results for this system have shown linear increases of droplet size with an increase of oil content at several fixed surfactant/cosurfactant concentrations within the microemulsion domain.

Introduction

Recent interest in the determination of the particle size of microemulsion systems has centred around the use of scattering techniques including small angle neutron scattering (Cebula et al., 1980, 1981, 1982; Caponetti and Magid, 1987), photon correlation spectroscopy (Cebula et al., 1981; Muller and Muller, 1984; Kizling and Stenius, 1987, Hou et al., 1988; Zulauf and Eicke, 1979; Chang and Kaler 1986) and time-average light scattering (Cebula et al., 1981, 1982; Baker et al., 1984; Cazabat et al., 1980). Problems may arise in the interpretation of scattering data because of strong interparticle interactions particularly when the systems are of high particle volume fraction. The usual procedure of extrapolation to zero concentration to remove the effects of non-ideality cannot usually be applied. Many microemulsions exhibit phase separation on dilution and even systems which remain clear may undergo transition to a micellar L region at high dilution (Baker et al., 1984). For systems where it is necessary to work in relatively high concentration regions it is essential to apply scattering theories which account for interparticle interaction.

Cebula et al. (1981) have presented an analysis of scattering data from water-in-oil microemulsions composed of water, xylene, sodium dodecyl benzene sulphonate and hexanol in which particle interactions were accounted for using the hard sphere model of Percus and Yevick (1958). Application of this treatment to both time-average light scattering and small angle neutron scattering data gave self-consistent results for particle size. Similar treatments were applied to light scattering data from this and other water-in-oil microemulsions by Cebula et al. (1982) and Baker et al. (1984). An

---

Correspondence: D. Attwood, Department of Pharmacy, University of Manchester, Manchester M13 9PL, U.K.

alternative approach developed by Caljé et al. (1977) relates osmotic compressibility (and hence intensity of scattered light) to the droplet parameters using a modification of the Percus-Yevick equations as proposed by Carnahan and Starling (1969). This approach has been applied in the analysis of intensity data for a series of water-in-oil microemulsions (Cazabat and Langevin, 1981; Brunetti et al., 1983; Bedwell and Gulari, 1984; Hou et al., 1988).

In this paper we have investigated oil-in-water microemulsions composed of isopropyl myristate, polysorbate 60, sorbitol and water. Phase studies have been conducted to show the influence of the polysorbate : sorbitol ratio on the extent of the microemulsion domain. Time-average light scattering data for systems with several fixed total concentrations of surfactant and cosurfactant have been analysed using the Percus-Yevick hard sphere model to determine the effect of variation of oil content on droplet size.

Materials and Methods

Materials

Polysorbate 60 (polyoxyethylene sorbitan monostearate, Tween 60), isopropyl myristate and D-sorbitol were used as supplied by Sigma Chemical Co.

Methods

Phase studies. The boundaries of the microemulsion domains were determined for a series of polysorbate : sorbitol mass ratios, R, by progressive titration of the 4 component mixtures. For each value of R, stock solutions of the components, each characterised by a selected mass ratio of isopropyl myristate to polysorbate and sorbitol, were progressively diluted with water in a stirred water-jacketed beaker at 55 ± 1° C. The samples were assessed visually to determine the regions of transparency. Samples prepared with compositions within the transparent microemulsion regions were stable for at least one month when stored at 37° C.

Preparation of samples for light scattering measurements. Three systems were examined containing 33.3%, 40.0% and 46.2% by weight of polysorbate 60 and sorbitol. In all systems the polysorbate : sorbitol mass ratio was maintained at 1 : 2. For each of the 3 systems, a series of microemulsions was prepared containing a range of concentrations of isopropyl myristate within the microemulsion domain as delineated in Fig. 1. The microemulsions were prepared by adding the required amount of a sorbitol solution of known concentration to mixtures containing weighed amounts of isopropyl myristate and polysorbate 60 in a stirred beaker at 55° C. Water was added, as required, from a burette. The microemulsions were equilibrated at 37° C and filtered through 0.22 μm Millipore filters before measurement.

Light scattering measurements. Measurements were performed at 37 ± 0.1° C using a Malvern 7027 laser light scattering instrument equipped with a 3 W Argon ion laser (Coherent Innova 90) operating at 488 nm. All measurements were at 90° to the incident beam. The instrument was calibrated with a dust-free sample of benzene (Analar) for which a Rayleigh ratio of 33.41×10^{-6} cm^{-1} was calculated for the wavelength and temperature used, from data of Gulari and Chu (1979).

Refractive index measurements. An Abbe 60/ED precision refractometer was used to determine the refractive index of the microemulsion samples at 37 ± 0.1° C. Measurements were performed at wavelengths of 589.3, 579, 546.1 and 535.8 nm and the refractive index at 488 nm interpolated from graphs of refractive index as a function of wavelength.

Results and Discussion

Phase studies. Ternary phase diagrams are presented in Fig. 1 to show the influence of the polysorbate 60 : sorbitol mass ratio on the area of existence of stable oil-in-water microemulsions. Only the microemulsion regions are shown, no attempt being made to characterise the phase properties in detail. Stable microemulsions with polysorbate : sorbitol mass ratios outside the range 1 : 1.5 to 1 : 4.0 could not be prepared under the experimental conditions of this study. A polysorbate : sorbitol mass ratio of 1 : 2 produced the largest microemulsion region and this ratio was

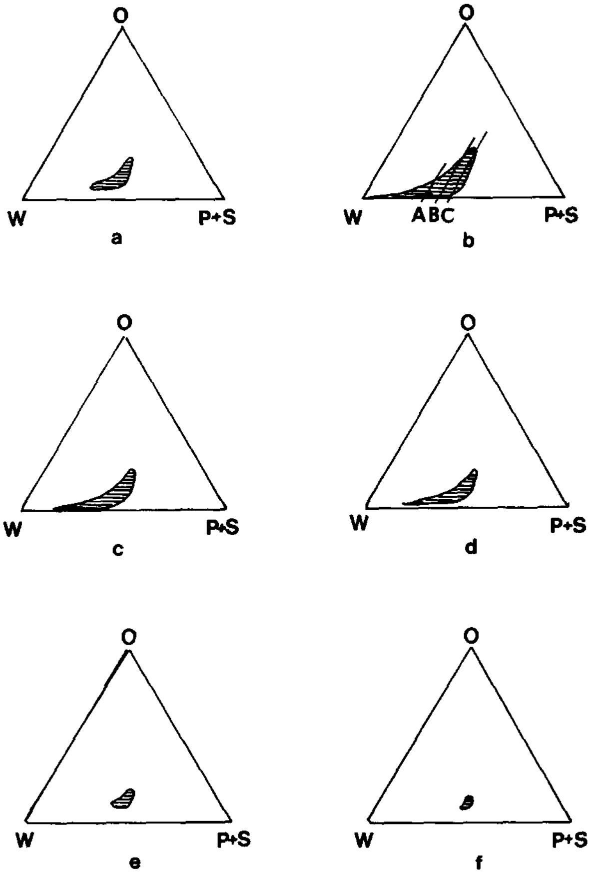

Fig. 1. Ternary phase diagrams of the system, isopropyl myristate (O), polysorbate 60 (P), sorbitol (S) and water (W) showing areas of existence of oil-in-water microemulsions at 37 °C for polysorbate : sorbitol mass ratios of: (a) 1 : 1.5; (b) 1 : 2.0; (c) 1 : 2.5; (d) 1 : 3.0; (e) 1 : 3.5; and (f) 1 : 4.0. Tie-lines along which microemulsions were investigated represent systems containing (A) 33.3%, (B) 40.0% and (C) 46.2% w/w of P + S.

selected for the preparation of microemulsions for particle size analysis.

In none of the systems studied did the microemulsion region extend fully into the water corner of the phase diagram. This inability to dilute the systems to infinite dilution necessitated the correction of light scattering data for interparticle interference in the determination of droplet size as discussed below.

Analysis of light scattering data

Total intensity light scattering measurements were carried out on microemulsions with composition given in Table 1. Results are shown in Fig. 2 as plots of the Rayleigh ratio at a scattering angle of 90 °, R_{90}, as a function of ϕ_0, where ϕ_0 is the volume fraction of isopropyl myristate, calculated from the weight % of this component and the densities of the isopropyl myristate and the microemulsions as determined by pycnometry.

The Rayleigh ratio at a scattering angle of θ for unpolarised light can be written in the general form:

$$R_\theta = (1 + \cos^2\theta) K_0 McP(Q)S(Q) \qquad (1)$$

where M is the molecular mass of the scattering particles, c is the concentration of dispersed particles and K_0 is an optical constant defined by:

$$K_0 = \frac{9\pi^2 n^4}{2N_A \lambda_0^4 \rho_c^2}\left[\frac{n_c^2 - n^2}{n_c^2 + 2n^2}\right]^2 \qquad (2)$$

where n and n_c are the refractive indices of the medium and of the scattering unit, respectively, N_A is the Avogadro constant, λ_0 is the wavelength

TABLE 1

Composition of microemulsions

Designation	Wt. % * (Polysorbate + sorbitol)	Wt. % Isopropyl myristate	Wt. % H_2O	Ref. index n^{37}_{488}
A1	33.3	1.7	65.0	1.3886
A2		2.2	64.5	1.3892
A3		2.8	64.9	1.3899
A4		3.3	63.4	1.3906
A5		3.9	62.8	1.3913
A6		4.4	62.3	1.3920
B1	40.0	2.7	57.3	1.4013
B2		3.3	56.7	1.4020
B3		4.0	56.0	1.4027
B4		4.7	55.3	1.4034
B5		5.3	54.7	1.4041
B6		6.7	53.3	1.4055
C1	46.2	3.8	50.0	1.4095
C2		4.6	49.2	1.4102
C3		5.4	48.4	1.4109
C4		6.1	47.7	1.4115
C5		7.7	46.1	1.4129
C6		9.2	44.6	1.4143

* Polysorbate 60 : sorbitol wt. ratio = 1 : 2.

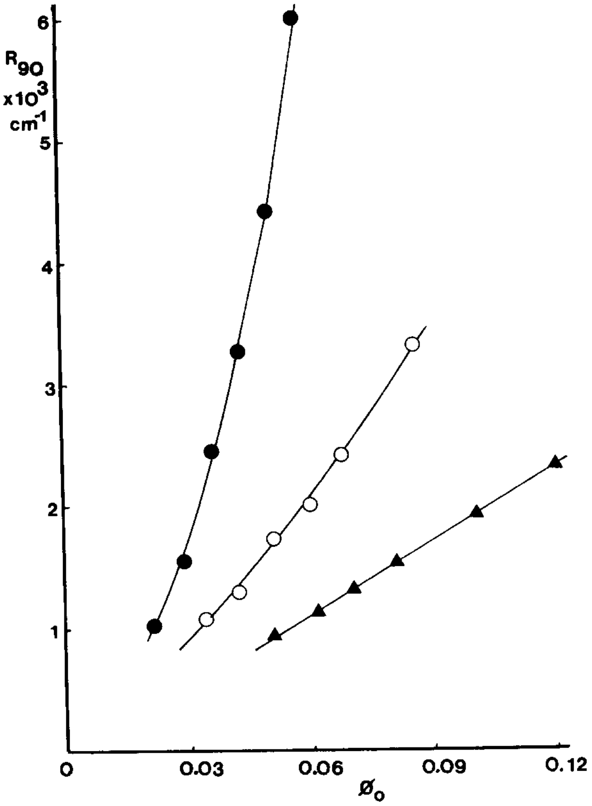

Fig. 2. Light scattering from microemulsions as a function of the volume fraction of isopropyl myristate, ϕ_0, for systems containing (●) 33.3%, (○) 40% and (▲) 46.2% by weight of polysorbate and sorbitol.

of incident light in vacuo and ρ_c is the density of the scattering units. The particle scattering form factor, $P(Q)$, for spherical particles is given by:

$$P(Q) = \left[3(\sin QR - QR \cos QR)/(Q^3R^3)\right]^2 \tag{3}$$

where Q is the scattering vector:

$$Q = 4\pi n \sin(\theta/2)/\lambda_0 \tag{4}$$

The structure factor, $S(Q)$, is a term which allows for interparticle interference due to interactions between the dispersed particles in these concentrated systems and is given by (Kerker, 1969):

$$S(Q) = 1 + \frac{4\pi N}{Q}\int_0^{\infty}(g(r)-1)r \sin Qr \, \mathrm{d}r \tag{5}$$

where N is the number of particles per unit volume, $g(r)$ is the particle-pair radial distribution function, with r equal to the distance between particle centres.

In the present work all the scattering measurements have been at $\theta = 90°$ for which Eqn. 1 reduces to:

$$R_{90} = K_0 McS(90)P(90) \tag{6}$$

Assuming that the scattering units are spherical with a radius R_c, then the molecular mass, M, of the particle is:

$$M = \tfrac{4}{3}\pi R_c^3 \rho_c N_A \tag{7}$$

If the volume fraction of the scattering unit is ϕ_c then $c = \phi_c \rho_c$ and Eqn. 6 becomes:

$$R_{90} = K_1 \phi_c R_c^3 S(90)P(90) \tag{8}$$

where

$$K_1 = K_0 4\pi N_A \rho_c^2/3 \tag{9}$$

or from Eqn. 2

$$K_1 = \frac{6\pi^3 n^4}{\lambda_0^4}\left[\frac{n_c^2 - n^2}{n_c^2 - 2n^2}\right]^2 \tag{10}$$

The calculation of R_c from Eqn. 8 requires a model of the microemulsion droplet and also a model by which the interparticle interaction may be quantified. Cebula and coworkers (1981, 1982) and Baker and coworkers (1984) have used the Percus-Yevick (1958) hard sphere model for the calculation of the interaction parameter, S(Q). The expression proposed by Ashcroft and Leckner (1966) for this parameter is:

$$S(Q) = \left[1 - Nc(2QR_{HS})\right]^{-1} \tag{11}$$

with

$$c(2QR_{HS}) = -32\pi R_{HS}^3 \int_0^1 \frac{\sin(2sQR_{HS})}{2sQR_{HS}} \times(\alpha + \beta s + \gamma s^3)s^2 \, \mathrm{d}s \tag{12}$$

where R_{HS} is the hard sphere radius and α, β and γ are coefficients defined by:

$$\alpha = (1 + 2\phi_{HS})^2/(1 - \phi_{HS})^4 \quad (13)$$

$$\beta = -6\phi_{HS}(1 + 0.5\phi_{HS})^2/(1 - \phi_{HS})^4 \quad (14)$$

$$\gamma = 0.5\phi_{HS}(1 + 2\phi_{HS})^2/(1 - \phi_{HS})^4 \quad (15)$$

In order to calculate the total fluid volume occupied by the spherical droplets, ϕ_{HS}, it is necessary to adopt a model of the dispersed particles. In view of the similarity of refractive indices of isopropyl myristate ($n_{488}^{37} = 1.434$) which forms the droplet core, and of the polysorbate 60 ($n_{488}^{37} = 1.468$) which forms an adsorbed layer around the droplet, it is not unreasonable to assume that these two regions constitute the scattering unit. Their combined radius has been equated with R_c of Eqn. 8 and the refractive index, n_c, has been assumed to be that of isopropyl myristate. There is an important difference between the model used in this present study and that adopted by Cebula et al. (1981). In the water-in-oil microemulsions studied by these workers, the scattering unit was clearly the water core of the droplet since the adsorbed surfactant layer had a refractive index more closely resembling the continuous medium (xylene) than the water of the core. ϕ_c in these systems could thus be equated with the volume fraction of water in the system. The calculation of ϕ_c for the scattering units of the oil-in-water microemulsions studied here is more complex since it involves an estimation of the quantity of surfactant associated with the droplets. To facilitate this calculation, the droplets were assumed to be monosized with an oil core radius, R_0, surrounded by a surfactant monolayer of vertically orientated polysorbate molecules. The quantity of surfactant (in grams), w_s, involved with the droplets was calculated from an assumed surface area, A, of a polysorbate molecule at the oil surface, using:

$$w_s = \frac{4\pi R_0^2}{A} \cdot \frac{M_s N_d}{N_A} \quad (16)$$

where M_s is the molecular mass of the surfactant. N_d is the total number of droplets, calculated from the weight, w_0, and density, ρ_0, of the isopropyl myristate using:

$$N = 3w_0/4\pi R_0^3 \rho_0 \quad (17)$$

The required volume fraction was given by:

$$\phi_c = (w_s/\rho_s + w_0/\rho_0)w/\rho \quad (18)$$

where w is the total weight of the components of the microemulsion and ρ_s and ρ are the densities of the surfactant and microemulsion, respectively. In this simplified working model of the droplet it has been assumed that the sorbitol, some of which will be interspersed between the hydrated polyoxyethylene chains of the adsorbed surfactant, does not contribute to the scattering unit and consequently has not been included in the calculation of ϕ_c. This outer shell of polyoxyethylene chains and sorbitol is, however, responsible for the interactions of the particles and allowance has been made for this in the calculation of the hard sphere radius. Assuming a thickness, t, of the outer layer, then:

$$R_{HS} = R_c + t \quad (19)$$

and the hard sphere volume is given by:

$$\phi_{HS} = \frac{R_{HS}^3}{R_c^3}\phi_c \quad (20)$$

An iterative method of calculation was used to determine combinations of the parameters R_0 and R_c giving the best representation of the experimental light scattering data for all 3 systems. Calculations were carried out for several values of A and t. For each of the selected values of these parameters, Eqn. 11 was integrated to give values of $S(Q)$ for a range of values of R_0 and R_c. R_{90} values, calculated by substitution into Eqn. 8, were compared with experimental R_{90} values and iteration was continued until satisfactory agreement between calculated and experimental values was obtained. Graphs of R_0 as a function of ϕ_0 and of R_c as a function of ϕ_c passed through the origin when an area per molecule, A, of 1 nm^2 was used (see Fig. 3). The agreement of this assumed value of A and the area per molecule at the air/water interface of approximately 0.8 nm^2 estimated from the surface tension data for polysorbate 60 reported by Wan and Lee (1974), provides some support for the assumptions made in these calculations.

The surfactant shell thickness, $R_c - R_0$, as indicated from these calculations was between 4 and 6 nm (see Table 2). Assuming that the polysorbate molecules within this shell are vertically orientated, then the maximum length of the C_{18} hydrocarbon chains which constitute the inner regions of the shell, would be 2.4 nm, as calculated from the expression, $\ell_{max} = 0.15 + (0.1265n)$, where n is the number of C atoms (Tanford, 1972). The outer regions of this shell contain the sorbitan moieties from which emanate the polyoxyethylene chains. The probable width of this region is difficult to estimate because of the heterogeneity of the polyoxyethylene chains and uncertainty of their conformation. In their fully extended and meander forms polyoxyethylene chains have lengths of 0.35 nm per ethylene oxide unit (Tanford et al., 1977). Calculations based on these values give shell dimensions of approximately the same magnitude of those of Table 2, giving further support to this simplistic model of the droplet.

TABLE 2

Radius of oil core, R_0, and total radius, R_c, of scattering units as calculated using $t = 0.6$ nm and $A = 1.0$ nm^2

Designation	Vol. fract. oil, ϕ_0	R_0 (nm)	Vol. fract. scatt. unit ϕ_c	R_c (nm)	$R_c - R_0$ (nm)
A1	0.022	4.0	0.055	8.2	4.2
A2	0.029	4.8	0.065	9.2	4.4
A3	0.036	6.3	0.071	10.8	4.5
A4	0.043	7.4	0.079	11.8	4.4
A5	0.050	8.4	0.087	13.0	4.6
A6	0.057	9.8	0.093	14.5	4.7
B1	0.035	4.0	0.090	9.8	5.8
B2	0.043	4.6	0.103	10.4	5.8
B3	0.052	5.8	0.109	11.6	5.8
B4	0.061	6.6	0.119	12.4	5.8
B5	0.070	7.5	0.128	13.3	5.8
B6	0.087	9.4	0.146	15.2	5.8
C1	0.052	5.3	0.113	11.1	5.8
C2	0.062	6.2	0.125	12.0	5.8
C3	0.072	7.0	0.137	12.9	5.9
C4	0.082	7.9	0.148	13.9	6.0
C5	0.102	9.7	0.170	15.7	6.0
C6	0.122	11.8	0.190	17.8	6.0

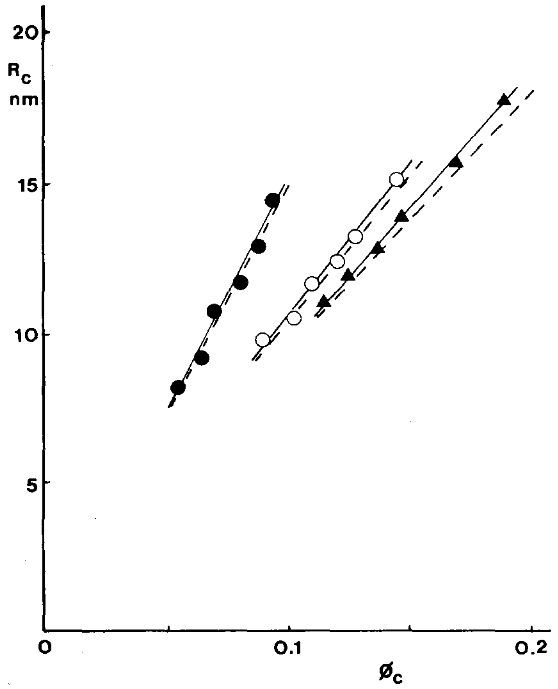

Fig. 3. Droplet core radius R_c, (calculated for $t = 0.8$ nm) as a function of volume fraction of core, ϕ_c, for systems containing (●) 33.3%, (○) 40.0% and (▲) 46.2% by weight of polysorbate and sorbitol. Values calculated for $t = 0.3$ nm are represented by (- - - - - -).

At each surfactant/cosurfactant concentration, the droplet radius R_c increased linearly with increase in the volume fraction ϕ_c (Fig. 3). Moreover, at a given value of ϕ_c the droplet size decreased with increase in the concentration of surfactant and cosurfactant in the system. Similar results were reported for the water-in-oil microemulsions studied by Baker et al. (1984), Cebula et al. (1981), Chang and Kaler (1986) and Hou et al. (1988).

References

Ashcroft, N.W. and Leckner, J., Structure and resistivity of liquid metals. *Phys. Rev.*, 145 (1966) 83–90.

Baker, R.C., Florence, A.T., Tadros, Th.F. and Wood, R.M., Investigations into the formation and characterisation of microemulsions. *J. Colloid Interface Sci.*, 100 (1984) 311–331, 332–349.

Bedwell, B. and Gulari, E., Electrolyte-moderated interactions in water/oil microemulsions. *J. Colloid Interface Sci.*, 102 (1984) 88–100.

Brunetti, S., Roux, D., Bellocq, A.M., Fourche, G. and Bothorel, P., Micellar interactions in water-in-oil microemulsions. 2. Light scattering determination of the second virial coefficient. *J. Phys. Chem.* 87 (1983) 1028–1034.

Caljé, A.A., Agterof, W.G.M. and Vrij, A., Light scattering of a concentrated water-in-oil microemulsion; application of modern fluid theories. In Mittal, K.L. (Ed.), *Micellization, Solubilization, Microemulsions, Vol. 2*, Plenum, New York, 1977, pp. 779–790.

Caponetti, E. and Magid, L.J., Static SANS measurements on concentrated water-in-oil microemulsions. In Rosano, H.L. and Clausse, M. (Eds.), *Microemulsion Systems, Surfactant Science Series, Vol. 24*, Marcel Dekker, New York, 1987, pp. 277–298.

Carnahan, N.F. and Starling, K.E., Equation of state for nonattracting rigid spheres. *J. Chem. Phys.*, 51 (1969) 635–636.

Cazabat, A.M., Langevin, D. and Pouchelon, A., Light scattering study of water-in-oil microemulsions. *J. Colloid Interface Sci.*, 73 (1980) 1–12.

Cazabat, A.M. and Langevin, D., Diffusion of interacting particles: light scattering study of microemulsions. *J. Chem. Phys.*, 74 (1981) 3148–3158.

Cebula, D.J., Harding, L., Ottewill, R.H. and Pusey, P.N., The structure of a microemulsion droplet. *Colloid Polymer Sci.*, 258 (1980) 973–976.

Cebula, D.J., Ottewill, R.H., and Ralston, J., Investigations of microemulsions by light scattering and neutron scattering. *J. Chem. Soc., Faraday Trans. I*, 77 (1981) 2585–2612.

Cebula, D.J., Myers, D.Y. and Ottewill, R.H., Studies on microemulsions. 1. Scattering studies on water-in-oil microemulsions. *Colloid Polymer Sci.*, 260 (1982) 96–107.

Chang, N.J. and Kaler, E.W., Quasi-elastic light scattering study of five component microemulsions. *Langmuir*, 2 (1986) 184–190.

Gulari, E. and Chu, B., Characterisation of meningococcal polysaccharides by light scattering spectroscopy. *Biopolymers*, 18 (1979) 2943–2961.

Hou, M.J., Kim, M. and Shah, D.O., A light scattering study on the droplet size and interdroplet interaction in microemulsions of AOT–oil–water system. *J. Colloid Interface Sci.*, 123 (1988) 398–412.

Kerker, M., *The Scattering of Light*, Academic, New York, 1969.

Kizling, J. and Stenius, P., Microemulsions formed by water, aliphatic hydrocarbons and pentaethylene glycol dodecyl ether: the temperature dependence of aggregate size. *J. Colloid Interface Sci.*, 118 (1987) 482–492.

Muller, B.W. and Muller, R.H., Particle size distributions and particle size alterations in microemulsions. *J. Pharm. Sci.*, 73 (1984) 919–922.

Percus, K.J. and Yevick, G.J., Analysis of classical statistical mechanics by means of collective co-ordinates. *Phys. Rev.*, 110 (1958) 1–13.

Tanford, C., Micelle shape and size. *J. Phys. Chem.*, 76 (1972) 3020–3024.

Tanford, C., Nozaki, Y. and Rohde, M.F., Size and shape of globular micelles formed in aqueous solutions by *n*-alkyl polyoxyethylene ethers. *J. Phys. Chem.*, 81 (1977) 1555–1560.

Wan, L.S.C. and Lee, P.F.S., CMC of polysorbates. *J. Pharm. Sci.*, 63 (1974) 136–137.

Zulauf, M. and Eicke, H.F., Inverted micelles and microemulsions in the ternary system H_2O/aerosol OT/isooctane as studied by photon correlation spectroscopy. *J. Phys. Chem.*, 83 (1979) 480–486.