

IJP 02992

A study on factors influencing the droplet size in nonionic oil-in-water microemulsions

D. Attwood^a, C. Mallon^a, G. Ktistis^b and C.J. Taylor^c

^a *Department of Pharmacy, University of Manchester, Manchester (UK)*, ^b *Pharmaceutical Technology, Department of Pharmacy, Aristotelean University of Thessaloniki, Thessaloniki (Greece)* and ^c *Lilly Research Centre, Windlesham, Surrey (UK)*

(Received 8 June 1992)

(Accepted 3 August 1992)

Key words: Microemulsion; Light scattering

Summary

The droplet size in oil-in-water microemulsions formed from isopropyl myristate (IPM), sorbitol (S), water and either polysorbate (P) 80, 60 or 40 was determined by total intensity light scattering measurements. Data were analysed using a hard-sphere model to correct for interparticle interactions. Phase studies on systems prepared using P40 have shown an optimum P/S mass ratio of 1:1.5 for microemulsion formation. The droplet size of all microemulsions increased with increasing volume fraction of IPM. At a given IPM content the droplet size was influenced by the structure of the polysorbate, the P/S ratio and the total P + S content. At a constant P/S ratio, the droplet size decreased with change of surfactant in the series P80 > P60 > P40. For microemulsions prepared with each polysorbate, change of the P/S ratio in the series 1:3, 1:2.5, 1:2, 1:1.5 caused a progressive decrease of droplet size. An increase of total P + S content from 40 to 45% w/w at a P/S ratio of 1:2.5 caused a decrease of the droplet size in microemulsions prepared with P80.

Introduction

The small size of the dispersed droplets of microemulsions, (typically less than 100 nm), necessitates the use of scattering techniques such as small angle neutron scattering, photon correlation spectroscopy and time-average light scattering in the particle sizing of these systems. In a previous study (Attwood and Ktistis, 1989), we reported the use of time-average light scattering methods in the determination of droplet size in oil-in-water microemulsions formed from iso-

propyl myristate (IPM), polysorbate 60 (P60), sorbitol (S) and water (W). In common with many microemulsions, these systems could not be diluted to infinite dilution without phase separation. Consequently, to allow meaningful calculation of droplet diameter, it was necessary to correct scattering measurements in high concentration regions for the nonideality arising from interparticle interaction. These corrections were performed using a hard-sphere model (Percus and Yevick, 1958), a model which had previously been applied to water-in-oil systems (Cebula et al., 1981, 1982; Baker et al., 1984).

We have now extended these studies to determine the influence of several formulation variables on the particle size of similar microemul-

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

sions prepared using polysorbates 80, 60 and 40. In particular, we report on the effect of the relative quantities of surfactant (polysorbate) to cosurfactant (sorbitol) (P/S ratio), the total content of surfactant and cosurfactant (P + S) and the nature of the surfactant.

Materials and Methods

Materials

Polysorbate 80 (polyoxyethylene (20) sorbitan monooleate, Tween 80), polysorbate 60 (polyoxyethylene (20) sorbitan monostearate, Tween 60), polysorbate 40 (polyoxyethylene (20) sorbitan monopalmitate, Tween 40), 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 the polysorbate 40, isopropyl myristate, sorbitol, water system for a series of P/S mass ratios. For each P/S ratio, the required quantities of polysorbate and IPM were warmed to about 60°C to form a monophasic mixture and slowly titrated with an aqueous sorbitol solution of the required concentration in a stirred, water-jacketed beaker at $55 \pm 1^\circ\text{C}$. The samples were assessed visually to determine the regions of transparency. Samples prepared with compositions within the transparent microemulsion region were stable for at least 1 month when stored at 37°C.

Light scattering measurements Measurements were performed at $37 \pm 0.1^\circ\text{C}$ 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 performed at 90° to the incident beam on samples filtered through $0.22 \mu\text{m}$ Millipore filters until dust-free. The instrument was calibrated with a dust-free sample of benzene (Analar).

Refractive index measurements An Abbe 60/ED precision refractometer was used to determine the refractive index of the microemulsions at $37 \pm 0.1^\circ\text{C}$. Measurements were performed at wavelengths, λ_0 , of 589.3, 579, 546.1

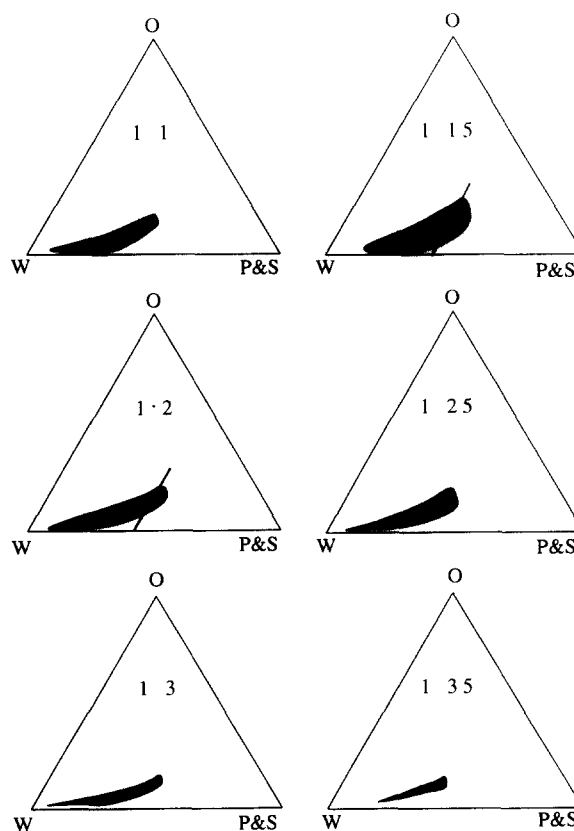


Fig. 1 Ternary phase diagrams of the system, isopropyl myristate (O), polysorbate 40 (P), sorbitol (S) and water (W) showing areas of existence of oil-in-water microemulsions at the polysorbate/sorbitol mass ratios indicated. Dilution lines represent systems containing a total P + S concentration of 40%

and 535.8 nm and the refractive index at 488 nm interpolated from linear plots of refractive index as a function of λ_0^{-2} .

Results and Discussion

Phase studies

Ternary phase diagrams are presented in Fig. 1 to show the influence of the P/S mass ratio on the area of existence of stable oil-in-water microemulsions prepared using P40. The diagrams show only the microemulsion regions, no attempt having been made to characterise the phase properties in any further detail. The largest microemulsion region was obtained using a P/S

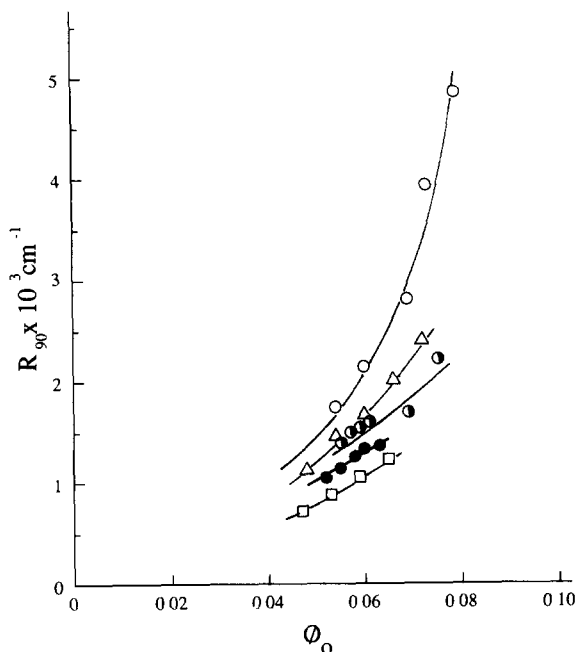


Fig. 2. Light scattering from P80/IPM/S/W microemulsions as a function of the volume fraction of IPM, ϕ_0 , for systems with P/S mass ratios of (\square) 1:1.5, (Δ) 1:2.0; (\circ) 1:2.5 containing a total P+S of 40%; and with P/S mass ratios of 1:2.5 and a total P+S of (\bullet) 43% and (\bullet) 45%.

mass ratio of 1:1.5. The use of ratios outside the range 1:1–1:3.5 did not result in significant microemulsion formation.

Comparison of the phase diagrams of Fig. 1 with those previously reported for P80/IPM/S/W (Ktistis, 1990) and P60/IPM/S/W (Attwood and Ktistis, 1989), highlights the influence of the nature of the polysorbate on phase properties. It is noted that the optimum P/S ratio for the formation of the largest microemulsion region is 1:2.5 for P80, 1:2.0 for P60 and 1:1.5 for P40. P80, which is an ester of the unsaturated C_{18} fatty acid, oleic acid, is more effective in forming a microemulsion than P60, which is an ester of the saturated C_{18} fatty acid, stearic acid, reflecting differences in the molecular packing at the oil/water interface. A larger proportion of the shorter chain fatty acid surfactant, P40, (ester of palmitic acid, C_{14}) is required for an optimum ratio.

Light scattering studies

Total intensity light scattering measurements were performed on systems of constant total concentration of P and S with a fixed P/S ratio and variable concentration of IPM. Fig. 1 shows the dilution lines representing systems with 40% total P40 and S at P/S ratios of 1:2 and 1:1.5. Similar dilution lines were used for P80 and P60 for a range of P/S ratios at a total P + S concentration of 40%. In systems prepared with P80, P + S concentrations of 43 and 45% were also examined. Figs 2–4 show the data for each polysorbate system plotted as the Rayleigh ratio R_{90} at a scattering angle, $\theta = 90^\circ$, as a function of ϕ_0 , where ϕ_0 is the volume fraction of IPM calculated from the weight % of this component and the densities of IPM and the microemulsions as determined by pycnometry.

In none of the systems studied was it possible to dilute to infinite dilution because of significant

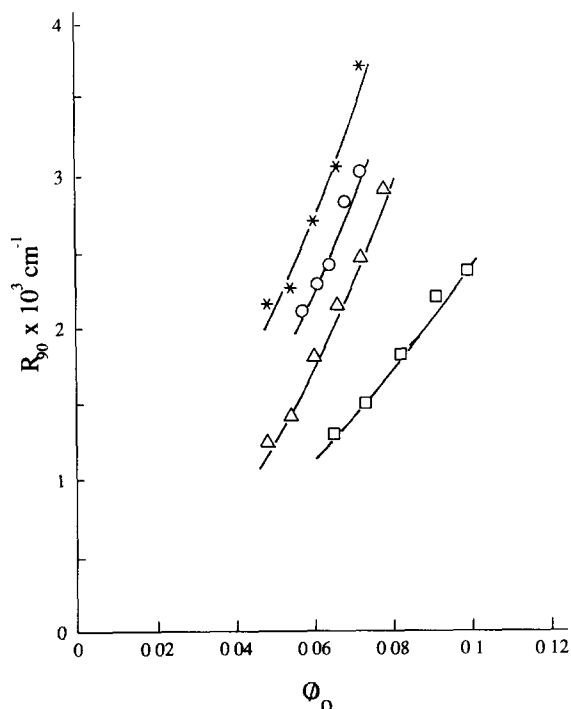


Fig. 3. Light scattering from P60/IPM/S/W microemulsions as a function of the volume fraction of IPM, ϕ_0 , for systems with P/S mass ratios of (\square) 1:1.5, (Δ) 1:2.0; (\circ) 1:2.5 and ($*$) 1:3.0 and containing a total P + S of 40%.

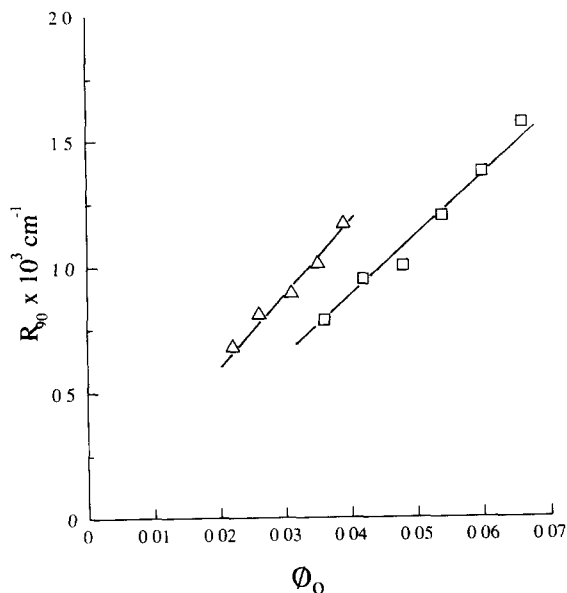


Fig. 4 Light scattering from P40/IPM/S/W microemulsions as a function of the volume fraction of IPM, ϕ_0 , for systems with P/S mass ratios of (\square) 1:1.5 and (\triangle) 1:2.0 and containing a total P+S of 40%

increases of turbidity for compositions outside the microemulsion regions. As a consequence, it was necessary to correct the data for interparticle interference in the determination of droplet size, as discussed by Attwood and Ktistis (1989).

The Rayleigh ratio, R_{90} , for unpolarised light is related to the volume fraction, ϕ_c , of the scattering unit (assumed to be spherical) by

$$R_{90} = K\phi_c R_c^3 S(Q)P(Q) \quad (1)$$

where K is an optical constant given by

$$K = \frac{6\pi^3 n^4}{\lambda_0^4} \left[\frac{n_c^2 - n^2}{n_c^2 - 2n^2} \right]^2 \quad (2)$$

where n_c and n are the refractive indices of the scattering unit and the medium, respectively, at the wavelength of incident light, λ_0 . The particle scattering factor, $P(Q)$, for spherical particles is

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

where Q is the scattering vector ($Q = 4\pi n \sin(\theta/2)/\lambda_0$). The structure factor, $S(Q)$, allows for nonideality due to interparticle interference and was calculated using the expression proposed by Ashcroft and Leckner (1966) based on the Percus-Yevick (1958) hard-sphere model.

$$S(Q) = [1 - Nc(2QR_{HS})]^{-1} \quad (4)$$

where N is the number of particles per unit volume and R_{HS} denotes the hard-sphere radius, which is related to the effective droplet radius, R_c , by $R_{HS} = R_c + t$. t is the thickness of the outer shell of polyoxyethylene chains and sorbitol molecules which are responsible for the interactions of the particles.

Eqns 1-4 have been applied by several workers (Cebula et al., 1981, 1982; Baker et al., 1984) in the determination of droplet size in water-in-oil microemulsions. Their application to oil-in-water

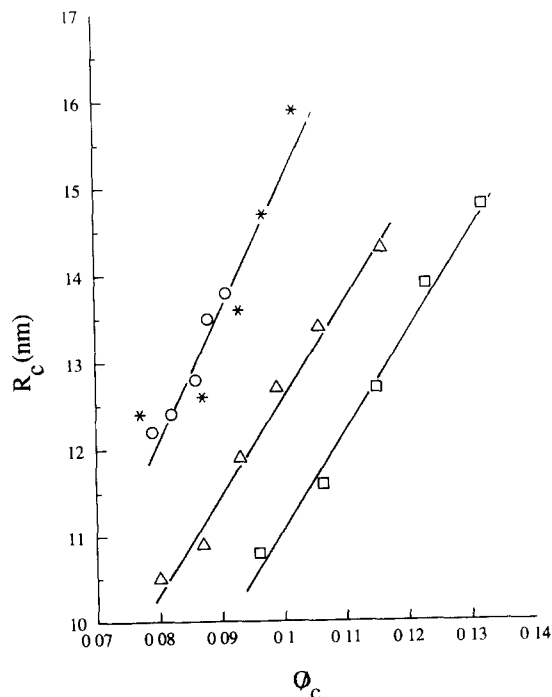


Fig. 5. Radius of scattering unit, R_c , as a function of its volume fraction, ϕ_c , for P60/IPM/S/W microemulsions with P/S mass ratios of (\square) 1:1.5; (\triangle) 1:2.0, (\circ) 1:2.5 and ($*$) 1:3.0 and with a total P+S of 40%

systems is less straightforward because of uncertainties in the constitution of the scattering units. The structure factor, $S(Q)$, as defined by Eqn 4, is a complex function of the volume ϕ_c of the dispersed droplets. In water-in-oil systems, the scattering units are clearly the water cores of the droplets, since the adsorbed surfactant layer usually has a refractive index similar to that of the continuous medium (Cebula et al., 1980). In contrast, the adsorbed layer of polysorbate molecules is of similar refractive index to that of the isopropyl myristate core and hence forms part of the scattering unit. However, the proportion of the total surfactant which surrounds the droplets is not known and hence ϕ_c cannot be directly calculated. Since an iterative method was used for the solution of the scattering equations, it was sufficient to supply an initial approximate estimation of this parameter. For this purpose, the quantity

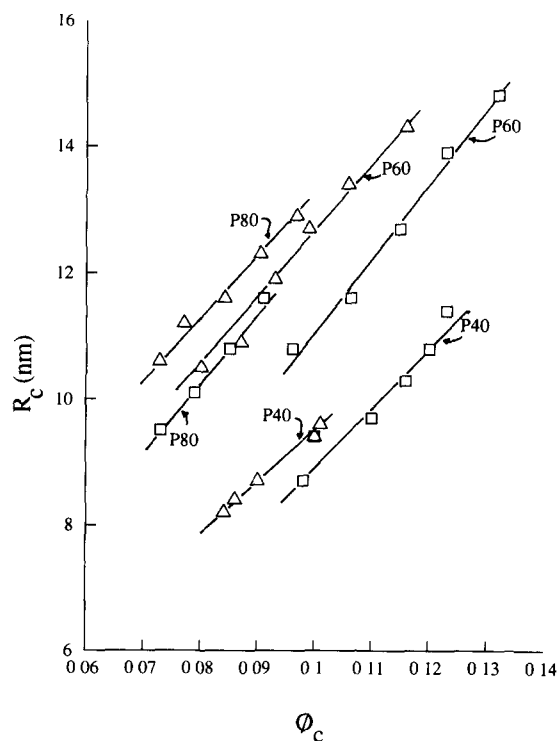


Fig 6 Radius of scattering unit, R_c , as a function of its volume fraction, ϕ_c , for microemulsions prepared using P80, P60 and P40 at P/S mass ratios of (\square) 1:1.5 and (\triangle) 1:2.0 and with a total P+S of 40%.

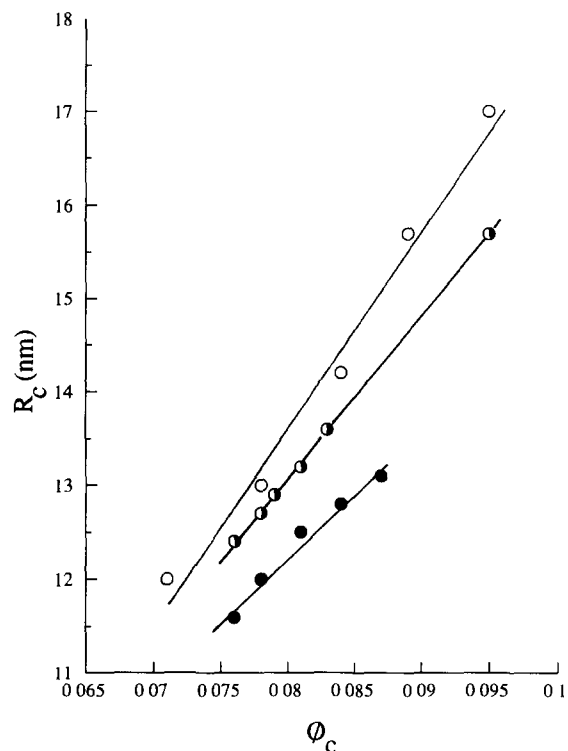


Fig 7. Radius of scattering unit, R_c , as a function of its volume fraction, ϕ_c , for P80/IPM/S/W microemulsions with a P/S mass ratio of 1:2.5 and with total P+S of (\circ) 40%; (\bullet) 43% and (\circ) 45%

of surfactant involved with the droplets was calculated assuming the surfactant to form a monolayer around the droplets and to occupy a surface area similar to that occupied by each surfactant at the air/water interface. The total surface area of the droplets was calculated assuming them to be monosized. In this simplified scheme no allowance was made for the contribution of the sorbitol to ϕ_c although molecules of this cosurfactant will of course, be interspersed between the hydrated polyoxyethylene chains of the outer shell.

The combinations of the parameters R_0 and R_c giving the best representation of the experimental light scattering data were determined by iterative calculation. $S(Q)$ was calculated for a range of values of R_0 and R_c from Eqn 4 and the resultant R_{90} values from Eqn 1 were compared with experimental values until satisfactory agreement was obtained.

Fig. 5 shows the variation of the droplet radius, R_c , with the volume fraction of the dispersed droplets for microemulsions prepared using P60. Similar graphs were obtained for P80 and P40 systems. At each P/S ratio, R_c is seen to increase linearly with increase of ϕ_c . A similar effect has been reported by many other workers using a variety of experimental techniques and several oil-in-water and water-in-oil microemulsions (see, for example, Sjoblom and Friberg (1978), Cebula et al. (1981), Chang and Kaler (1986), Attwood and Ktistis (1989)). Moreover, at a given value of ϕ_c , the droplet size decreased as the P/S ratio was altered from 1:3 to 1:1.5, i.e., as the proportion of sorbitol in the surfactant/cosurfactant mixture was decreased. These results are in agreement with those of Kale and Allen (1989) who noted a similar decrease in droplet size in oil-in-water microemulsions prepared using Brij 96 as surfactant and either glycerin, ethylene glycol or propylene glycol as cosurfactant.

The influence of the surfactant structure on droplet size is shown in Fig. 6 for microemulsions prepared with P80, P60 and P40 with P/S ratios of 1:1.5 and 1:2. This figure shows for each P/S ratio, a small, but significant, decrease in droplet radius at a given ϕ_c value in the order P80 > P60 > P40.

It may be seen from Fig. 7 that at a given volume fraction, the droplet size of microemulsions prepared using P80 with a P/S ratio of 1:2.5, decreased with increase in the total surfactant and cosurfactant content from 40 to 45% w/w. These results are in agreement with those reported previously (Attwood and Ktistis, 1989) for the P60 system. Similar effects have been reported for water-in-oil microemulsions by Baker et al. (1984), Chang and Kaler (1986) and Hou et al. (1988).

Acknowledgment

The authors thank Lilly Research Co. for generous financial support.

References

- Ashcroft, N W and Leckner, J, Structure and resistivity of liquid metals. *Phys. Rev.*, 145 (1966) 83–90.
- Attwood, D and Ktistis, G., A light scattering study on oil-in-water microemulsions. *Int J Pharm.*, 52 (1989) 165–171
- Baker, R C, Florence, A T., Tadros, T F. and Wood, R.M., Investigations into the formation and characterisation of microemulsions *J Colloid Interface Sci.*, 100 (1984) 311–331, 332–349
- Cebula, D.J., Harding, L, Ottewill, R.H and Pusey, P N., The structure of a microemulsion droplet *Colloid Polym Sci.*, 258 (1980) 973–976
- Cebula, D.J, Myers, D Y. and Ottewill, R.H., Studies on microemulsions 1 Scattering studies on water-in-oil microemulsions. *Colloid Polym Sci.*, 260 (1982) 96–107
- 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
- Chang, N J and Kaler, E W, Quasi-elastic light scattering study of five component microemulsions. *Langmuir*, 2 (1986) 184–190.
- 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 systems *J Colloid Interface Sci.*, 123 (1988) 398–412
- Kale, N J. and Allen, L V, Studies on microemulsions using Brij 96 as surfactants and glycerin, ethylene glycol and propylene glycerol as cosurfactants *Int J Pharm.*, 57 (1989) 87–93
- Ktistis, G., A viscosity study on oil-in-water microemulsions *Int J Pharm.*, 61 (1990) 213–218.
- Percus, K J and Yevick, G J, Analysis of classical statistical mechanics by means of collective co-ordinates. *Phys Rev.*, 110 (1958) 1–13
- Sjoblom, E and Friberg, S.E., Light scattering and electron microscopy determinations of association structures in water-in-oil microemulsions *J Colloid Interface Sci.*, 67 (1978) 16–30.