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Self-emulsifying drug delivery systems: assessment of the efficiency of emulsification

Colin W. Pouton *

Department of Pharmacy, Chelsea College, University of London, London SW3 6LX (U.K.)

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Summary

Self-emulsifying formulations have potential uses as vehicles for the administration of lipophilic drugs by the oral route. In this study model oil–surfactant mixtures were allowed to self-emulsify under conditions of gentle agitation. During emulsification the relative intensity of light scattered by the dispersion was monitored continuously which enabled the rates of emulsification to be compared. The particle sizes of resultant emulsions were compared by light microscopy and using a Coulter Nano-Sizer. Efficient self-emulsifying formulations were produced by the oils Miglyol 812 or Miglyol 840 in combination with the surfactant Tween 85. The properties of these systems have been studied over a range of mixture compositions. The finest dispersions were produced rapidly and in reproducible time by a mixture of 30% w/w Tween 85 and 70% w/w Miglyol 812.

Introduction

A 'self-emulsifying' system is a mixture of oil and surfactant which emulsifies in water under conditions of gentle agitation. Such mixtures may be spontaneously emulsifying if the entropy change favouring dispersion is larger than the energy required to increase the surface area of the dispersion (Reiss, 1975). In practice the occurrence of spontaneous emulsification is difficult to establish because when

* *Present address:* School of Pharmacy and Pharmacology, University of Bath, Bath BA2 7AY, U.K.

mechanical agitation is absent gravitational force provides a small quantity of energy for emulsification. For the purpose of pharmaceutical formulation it is not essential to identify those systems which are spontaneously emulsifying; it is more important to distinguish between self-emulsifying systems and conventional emulsion systems which will be finely dispersed only after exposure to strong shearing forces.

Self-emulsifying formulations have been used by the herbicide and pesticide industries for several years (Eaton, 1962; Hartley, 1967). Many commonly used herbicides have low solubilities in water which prevent their formulation as concentrated aqueous solutions. Concentrates of some sort are necessary because transportation of working solutions in bulk is impractical. Therefore lipophilic herbicides are dissolved in organic solvents with surfactants to produce self-emulsifying formulations which can be dispersed easily in local water prior to crop spraying. It has been suggested that self-emulsifying drug delivery systems can be prepared which, after oral administration in gelatin capsules, will emulsify within the gastric contents (Groves and de Galindez, 1976). Such a formulation will present a lipophilic drug in oily solution with a large interfacial area across which diffusion can take place. The mechanisms, rate and extent of drug absorption from the resulting emulsion will be strongly dependent on the oils and surfactants used in each formulation. For example, absorption will be influenced by whether or not the oil is digestible and by the partitioning of drug between the oil and water (Armstrong and James, 1980). In addition the surfactants may modify absorption by a variety of mechanisms (Attwood and Florence, 1983a). Therefore the absorption profiles of a drug from a series of self-emulsifying formulations are likely to be different but it is hoped that the absorption from an individual formulation will be comparatively reproducible, leading to improved control of the bioavailability of lipophilic drugs from the gastrointestinal tract. One advantage that self-emulsifying formulations have over solid dosage formulations is the avoidance of slow drug dissolution. In addition distribution of the emulsion within the gastrointestinal tract may help to avoid the irritancy which can be caused by contact between bulk solids and the gut wall.

Obviously the excipients used for formulation would need to be non-irritant and free from other acute or chronic toxicity problems. Choice of oils is likely to be restricted to silicones, liquid paraffin or vegetable oils and their derivatives. These could be used in combination with non-ionic surfactants which are generally less toxic than ionic surfactants (Attwood and Florence, 1983b).

Two criteria are proposed to describe the efficiency of self-emulsification: (a) the rate of emulsification; and (b) the particle size distribution of the resultant emulsion. There are no established methods available for the study of self-emulsification. Formulators in the pesticide industry have used subjective tests of quality (CIPAC, 1970). Groves and Mustafa (1974) have described an objective method for comparison of emulsification rate of self-emulsifying systems. The weakness of the above method was that no assessment of particle size was possible. In order to allow comparison of particle size during the present study the self-emulsification process took place in a glass cell described below. Gentle agitation was provided by a glass paddle so that the mixture remained homogeneous during emulsification but little

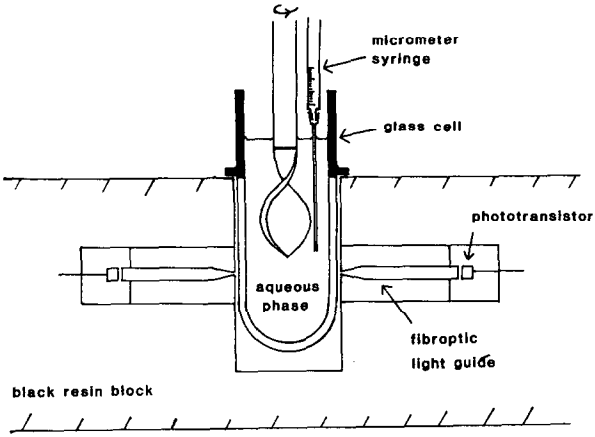

Fig. 1. Schematic diagram of the apparatus used for self-emulsification: cell and nephelometer in vertical cross-section. (Volume of aqueous phase = 15 ml; dimensions of glass paddle blade = 3.0 × 1.5 cm.)

shearing force was available to aid emulsification. A comparative measure of the rate of emulsification was obtained using nephelometry and the particle sizes of undiluted samples of emulsions were examined by light microscopy and using a Coulter Nano-Sizer.

Materials and Methods

Chemicals

Water was freshly distilled from an all-glass still. Polyoxyethylene (20) sorbitan trioleate (Tween 85 from Honeywill-Atlas), medium chain triglyceride oil (Miglyol 812 from Dynamit Nobel), medium chain diesters of propylene glycol (Miglyol 840 from Dynamit Nobel), light liquid paraffin (BDH), oleic acid 92% (BDH) and glyceryl trioleate (prepared from technical grade oleic acid, BDH) were used as received. Polystyrene latices of various nominal particle sizes were obtained from Dow, Rhone-Progil and Duke.

Description of the self-emulsification cell

Fig. 1 represents the cell and nephelometer in vertical cross-section. A glass cell sat within the nephelometric device which was mounted in a black resin block. The block could be raised by means of a laboratory jack to meet a glass paddle and micrometer syringe which were held in a fixed position by clamps attached to a metal frame. The frame in turn was bolted onto a wooden base which also held the laboratory jack and nephelometer block in a fixed position. The block was raised to the same position for each experiment such that the plane of the nephelometer was 1 cm below the tips of the paddle and syringe needle. Incident light was provided by a 55 W projector lamp via a flexible fibroptic light guide. The glass paddle was rotated

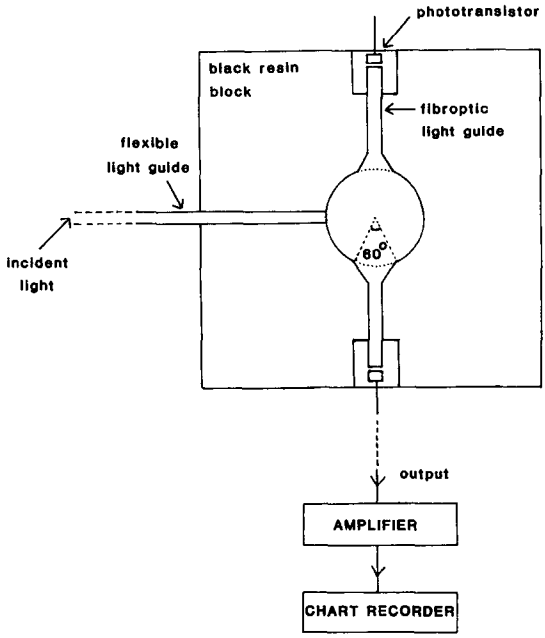

Fig. 2. Schematic diagram of the nephelometer in horizontal cross-section.

at a constant speed of 100 rpm (±1%) by an electric motor (Citenco KQPS.22) stabilized at low speed using a thyristor-controlled variable resistance (Trager). Emulsifiable material was injected by volume, at a fixed depth below the surface of 15 ml of aqueous phase contained within the cell, using an Agla micrometer syringe (Wellcome Res.) fitted with disposable needles (Sabre size 25-gauge × 15/16 inch from Gillette Surgical). Scattered light was gathered by fibroptic light guides mounted in the nephelometer block, as shown in Fig. 1 and in horizontal cross-section in Fig. 2. The relative intensity of scattered light was measured using a pair of phototransistors. The output from the phototransistors was amplified and plotted against time on a chart recorder.

Characterization of the nephelometer

The scattering of light by particulate dispersions is a complex subject which has been described in detail elsewhere (Jonker, 1952; Kerker, 1969). At its simplest, for small particles when no interparticulate interaction or multiple scattering occurs, light scattering by colloids conforms to Rayleigh theory. Larger particles scatter light according to Lorenz-Mie theory. Rayleigh theory predicts that the intensity of scattering D_θ in a direction which subtends an angle θ with the incident beam is given by,

$$D_\theta = \frac{9 \cdot \pi^2 \cdot N \cdot v^2}{2 \cdot d^2 \cdot \lambda^4} \cdot \frac{(n_1^2 - n_0^2)}{(n_1^2 + 2n_0^2)} \cdot (1 + \cos^2\theta) \cdot D_0 \qquad (1)$$

TABLE 1
LIGHT SCATTERING OF POLYSTYRENE LATICES

Mean particle diameter (μm)	(particle volume)^2 ($\mu m^3)^2 \times 10^6$	Relative $d(D_s)/dN$	Relative $d(D_s)/dC$	Correlation coefficient
0.21	24	2.2	4.3	0.9982
0.30	200	9.4	6.3	0.9990
0.34	424	16.9	8.0	0.9984
0.47	2955	57.9	10.2	0.9992
0.60	12790	177.7	15.0	0.9997
0.88	127300	446.1	11.9	0.9997
1.20	818600	657.4	6.9	0.9999

where D_0 is the intensity of the incident beam, v is the volume of a single particle, N is the particle number per unit volume, d is the distance between the point of measurement and the sample, λ is the wavelength of light and n_1 and n_0 are the refractive indices of the dispersed phase and the continuous phase. The nephelometer currently described simultaneously gathered scattered white light from many angles. However, for any set of measurements using the same instrument, similar conditions and materials many of the terms in the above equation are constant. The equation can be reduced to the form:

$$D_s = j \cdot N \cdot v^2 \tag{2}$$

where j is a machine constant and D_s is the total relative intensity of scattering. The properties of the nephelometer were tested using a series of polystyrene latices of narrow size range. The relative intensity of scattering was determined at various concentrations of each latex in order to calculate the slope $d(D_s)/dN$. The mean particle size of each latex was determined using a Coulter Nano-Sizer (see below). Table 1 summarizes the data obtained. If Rayleigh's equation held, then Eqn. 2 shows that a plot of $d(D_s)/dN$ against v^2 would be linear. In fact Rayleigh's work predicts that the theory would only hold if the particles were significantly smaller than the wavelength of the incident light (radius $< \lambda/20$). Therefore for latex diameters over the range 0.1–1 μm one would expect non-ideal behaviour. Fig. 3 shows a plot of log relative $d(D_s)/dN$ against log v^2. Unexpectedly the plot conformed to Eqn. 2 up to latex diameters of about 0.6 μm. The curve deviated from linearity as particle diameter approached 1.0 μm. Similar results have been reported of laser light scattering by polymer latices (Lee, 1980). Table 1 also includes the slope $d(D_s)/dC$ obtained from a plot of D_s against % w/w latex concentration. This parameter indicates the relationship between particle size and intensity of scattering in relation to the dispersion of a fixed mass of material. Thus if the quantity of self-emulsifying mixture remained constant then emulsions formed with mean sizes between 0.2 and 1.0 μm were expected to scatter light strongly. Low intensities of scattering were characteristic of very fine or coarse emulsions. For a given con-

Fig. 3.

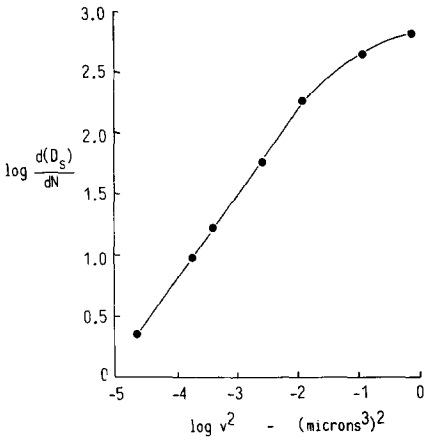

Fig. 4.

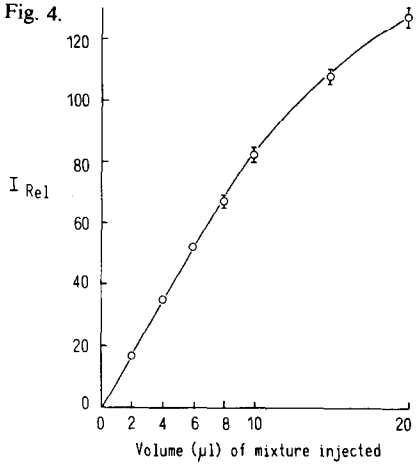

Fig. 3. Plot of log $d(D_s)/dN$ against log (particle volume)^2.

Fig. 4. Plot of relative intensity of light scattering (I_{Rel}) at equilibrium against volume of mixture injected. (70% w/w Miglyol 812/30% w/w Tween 85 in distilled water at 25°C. Mean ± S.D. n = 5.)

centration of dispersed phase, by weight, strong light scattering was typical of dispersions with mean particle sizes close to the wavelength of the incident light.

Self-emulsification procedure

15 ml aqueous phase was pipetted into the glass cell. The chart recorder was switched on and emulsifiable material was injected as described, noting the time of injection on the chart recording. When the emulsification procedure had reached an equilibrium the intensity of light scattering was constant (see below). Equilibrium for self-emulsifying systems was reached within one minute but agitation was continued for a standard time of ten minutes prior to particle size analysis unless the intensity of scattering was still changing after ten minutes, in which case the time period was extended accordingly. This was only necessary for some poorly-emulsifying systems. All experiments were carried out at 25 ± 0.5°C. The temperature was determined before and after emulsification.

Throughout the study the intensity of scattering at equilibrium was proportional to emulsion concentration over the working concentration range. Fig. 4 shows the effect of injection volume on the intensity of scattering at equilibrium for a representative self-emulsifying system. When the volume of the oil–surfactant mixture exceeded 10 µl the plot began to deviate from linearity. Therefore an injection volume of 10 µl emulsifiable material in 15 ml aqueous phase was adopted as standard.

The mixing efficiency of the paddle was tested using a preformed emulsion (Intralipid 20% from Kabi Vitrum). At rotor speeds greater or equal to 100 rpm, homogeneity was always achieved within 4 s, timed from the point of emulsion injection. These conditions were considered to be satisfactory.

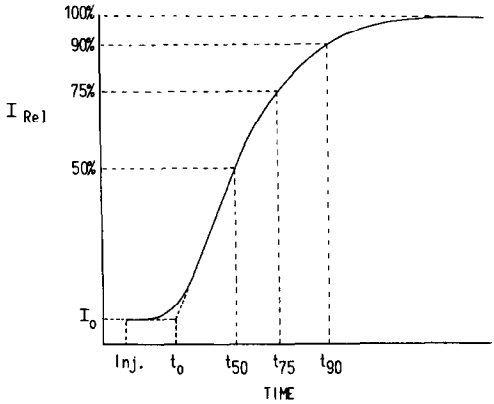

Fig. 5. General shape of plots of relative intensity of light scattering (I_{Rel}) against time during self-emulsification.

Determination of emulsification time

Plots of relative intensity of scattered light (I_{Rel}) against time during the emulsification process were similar to profiles of the dissolution of solids in aqueous media. Characteristically they consisted of a lag phase, a pseudo-linear phase and finally a gradual 'tailing' towards an asymptote as the emulsion system approached equilibrium. This type of plot for emulsion growth has been observed by Gopal (1968) using ultrasonication to provide energy for emulsification. The value of I_{Rel} was not a direct measure of the number of particles present or their particle size. Therefore mathematical modelling of I_{Rel} as a function of time was considered inappropriate. In order to compare the rates of emulsification the parameters shown in Fig. 5 were determined. The emulsification times t_0, t_{50}, t_{75} and t_{90} corresponded to the lag time and the times taken to reach 50%, 75% and 90% of the final intensity at equilibrium. Emulsification times were expressed as means and standard deviations of five replicates.

Preparation of homogenized emulsions

Homogenized emulsions of the same composition as self-emulsified systems were prepared to compare their particle sizes with self-emulsified systems. The densities of the emulsifiable oil–surfactant mixtures were determined using an Anton Paar densitometer (model DMA 45). A mass of each mixture equivalent to 0.133 ml was weighed into a 400 ml beaker. 200 ml distilled water was added and the mixture was emulsified at 25 ± 0.5°C for 15 min using a Silverson homogenizer at its lowest speed.

Assessment of emulsion particle size

No standard particle sizing technique was suitable for sizing all of the emulsions under examination. Efficiently self-emulsifying systems, which were of prime interest, resulted in dispersions which were substantially sub-micron in size. The Coulter Nano-Sizer, which automatically performs photon correlation analysis on scattered

TABLE 2
SELF-EMULSIFICATION TIMES OF MIGLYOL 812/TWEEN 85 MIXTURES IN DISTILLED WATER AT 25°C (MEAN ± S.D., n = 5)

Mixture composition (% w/w)		I_{Rel}	Emulsification times (seconds)			
Miglyol 812	Tween 85		t_0	t_{50}	t_{75}	t_{90}
80	20	80.0 ± 3.3	4.8 ± 0.4	9.1 ± 0.9	12.8 ± 2.7	19.1 ± 5.2
75	25	80.6 ± 2.3	3.6 ± 0.4	8.3 ± 0.7	11.2 ± 1.0	15.5 ± 1.8
70	30	81.7 ± 3.7	3.2 ± 0.3	6.5 ± 0.4	8.5 ± 0.8	11.3 ± 1.4
65	35	71.8 ± 1.9	3.0 ± 0.2	6.3 ± 0.4	8.2 ± 0.5	10.7 ± 0.9
60	40	56.2 ± 0.7	2.7 ± 0.3	5.8 ± 0.4	7.5 ± 0.4	9.1 ± 0.4
55	45	36.8 ± 1.7	2.1 ± 0.2	5.7 ± 0.4	8.0 ± 0.5	12.2 ± 2.4
50	50	20.4 ± 1.4	2.4 ± 0.7	8.7 ± 1.5	16.4 ± 4.9	32.9 ± 10.7
40	60	11.7 ± 0.8	3.0 ± 0.5	11.1 ± 1.4	20.5 ± 2.5	36.5 ± 5.0

light, was used to provide a comparative measure of mean particle size for such systems. This instrument detects dynamic changes in laser light scattering intensity which occur when particles oscillate due to Brownian motion. A mean particle size is computed for those particles between the approximate limits 40–3000 nm (Lines and Miller, 1979). The polydispersity index indicates the size range as a score between 0 and 9 (narrow to wide size ranges). When particles above 3 μm are present they are not detected and therefore not included in the computation. Thus if the Coulter Nano-Sizer is used to determine the mean particle size of a widely dispersed emulsion the result is likely to be misleading.

In the present study the mean particle sizes of undiluted emulsions were determined in triplicate using a Coulter Nano-Sizer. Emulsions were then examined by light microscopy to detect the presence of large particles which indicated when the use of the Coulter Nano-Sizer was inappropriate.

Results and Discussion

In comparison with a variety of isotropic oil–surfactant mixtures, certain compositions of Miglyol 812 and Tween 85 appeared to emulsify easily. Therefore the self-emulsification of mixtures of Miglyol 812 and Tween 85 was studied over a wide range of mixture compositions. Table 2 shows the values of I_{Rel} and emulsification times for mixtures dispersed in distilled water at 25°C. Values of I_{Rel} above 50 were typical of mixtures which formed emulsions of visibly good quality. Mixtures containing 0–15% w/w Tween 85 did not self-emulsify. Values of I_{Rel} for the latter systems were always below 5 units and after 10 min large droplets of oil were visible in the emulsification cell. Within a range of more efficiently emulsifying mixtures (20–60% w/w Tween 85) the shortest emulsification times occurred between 30 and 45% w/w Tween 85. Emulsification times lengthened considerably for compositions either side of the optimum range. Mixtures containing more than 60% w/w Tween 85 had long emulsification times, low I_{Rel} values and produced poor emulsions.

TABLE 3
APPARENT MEAN PARTICLE SIZE OF SELF-EMULSIFIED AND HOMOGENIZED EMULSIONS OF MIGLYOL 812/TWEEN 85 MIXTURES IN DISTILLED WATER AT 25°C (MEASURED USING A COULTER NANO-SIZER; MEAN ± S.D. OF 3 REPLICATE EXPERIMENTS)

Mixture composition (% w/w)		Self-emulsified systems			Homogenized systems		
Miglyol 812	Tween 85	Particle size (nm)		P.I. [a]	Particle size (nm)		P.I. [a]
		Mean	S.D.		Mean	S.D.	
85	15	320	22	7	380	18	4
80	20	310	3	2	235	6	3
75	25	287	3	2	210	4	3
70	30	278	2	2	189	2	1
65	35	295	2	4	176	6	3
60	40	321	12	5	182	6	2
55	45	423	25	7	186	7	3
50	50	487	24	8	182	7	3
40	60	562	33	9	180	5	4
0	100	–	–	–	135	1	4

[a] Polydispersity index.

Most Miglyol 812–Tween 85 systems which self-emulsified rapidly also produced emulsions which had small mean particle sizes (Table 3). A minimum in particle size for self-emulsified systems was produced by compositions of between 25% and 35% w/w Tween 85. When mixtures containing 0, 5 and 10% w/w Tween 85 were assessed using the self-emulsification procedure the resultant emulsions were too coarse to be analyzed using the Nano-Sizer. In such cases the instrument indicated that the mean particle size was indeterminate but > 3 μm. The mixture containing 15% w/w Tween 85 produced emulsions which were visibly poor but contained some particles sub-micron in diameter. When these were analyzed using the Nano-Sizer the apparent mean particle size was variable with a mean of 320 nm and a polydispersity index of 7. The high polydispersity index indicated that the droplet size distributions were wide and this was confirmed by microscopy (Fig. 6). For these systems the bulk of the oil was dispersed as droplets > 10 μm in diameter. Emulsions formed by self-emulsification of mixtures containing 20–30% w/w Tween 85 all had a polydispersity index of 2 indicating that their size distributions were comparitively narrow. When these emulsions were examined by microscopy very few particles above 5 μm in diameter could be detected which confirmed that their size distributions were indeed much narrower than emulsions formed by the 15% w/w mixture. Microscopic examination also suggested that the Nano-Sizer was an appropriate instrument for sizing emulsions formed by genuine self-emulsifying systems containing 20–35% w/w Tween 85 which were of prime interest to this study. When the concentration of Tween 85 in the oil–surfactant mixture was increased from 35 to 60% w/w the mean particle size of self-emulsified systems increased markedly. In addition the mean particle size became less reproducible as shown by the increase in standard deviation of the mean of replicate experiments and there was a gradual widening of the size distributions indicated by the increase in

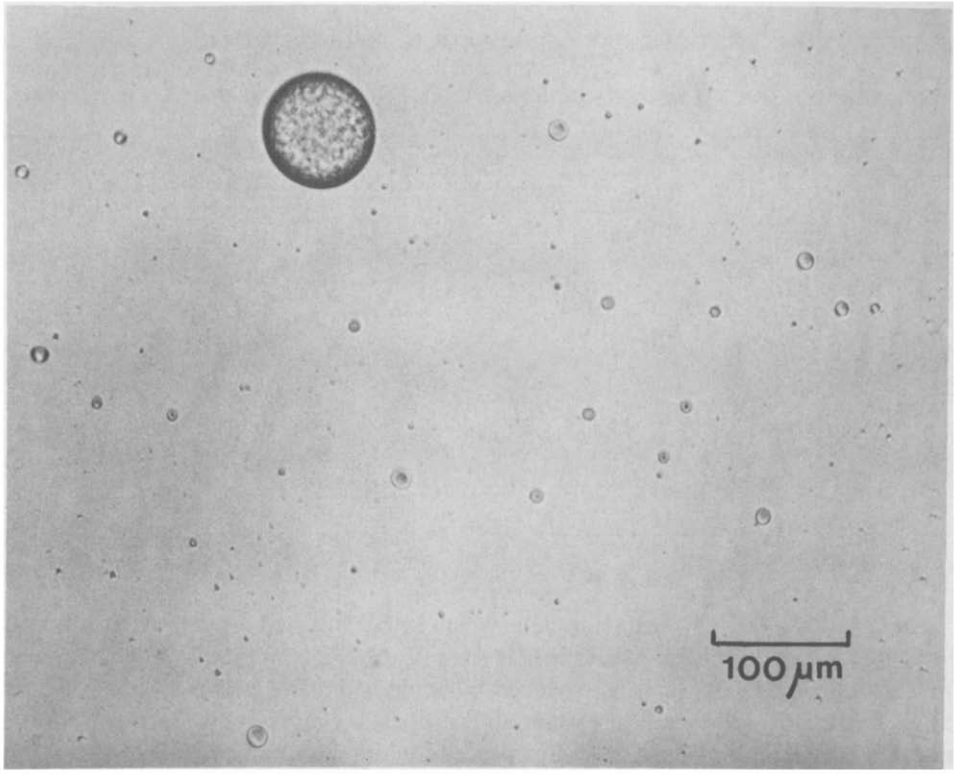

Fig. 6. Photomicrograph of a typical emulsion formed by self-emulsification of a 15% w/w Tween 85 mixture in distilled water at 25°C.

polydispersity index (Table 3). Microscopic examination of emulsions formed by mixtures containing $\geqslant$ 45% w/w Tween 85 confirmed that their size distributions were wide. Fig. 7 is a photomicrograph of a typical emulsion formed by self-emulsification of the mixture containing 45% w/w Tween 85 which shows that a considerable proportion of the oil was dispersed as particles > 10 μm in diameter. Mixtures containing > 60% w/w Tween 85 emulsified slowly in the self-emulsification cell to produce extremely coarse dispersions which were of no interest and therefore were not further investigated.

A series of emulsions corresponding to the self-emulsified systems were prepared by the homogenization process (Table 3). Homogenized emulsions formed by mixture containing 0, 5 and 10% w/w Tween 85 were too coarse to be sized by the Nano-Sizer as were the corresponding self-emulsified systems. The homogenized system formed by the 15% w/w Tween 85 mixture had a larger apparent mean particle size (380 nm) than the corresponding self-emulsified system (320 nm) although the polydispersity index of the homogenized system was lower suggesting that a larger proportion of particles of the homogenized system were of sub-micron diameters. When the Tween 85 content of the mixture was $\geqslant$ 20% w/w the mean

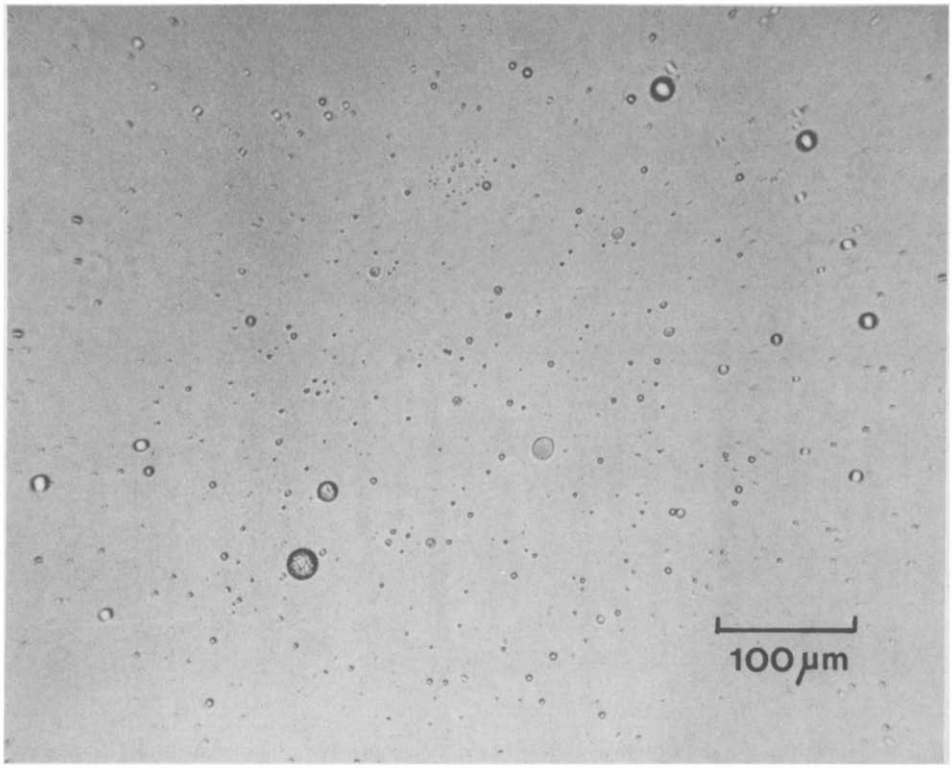

Fig. 7. Photomicrograph of a typical emulsion formed by self-emulsification of a 45% Tween 85 mixture in distilled water at 25°C.

particle size of each homogenized system was smaller than that of the corresponding self-emulsified system. There was no significant difference between homogenized systems formed by mixtures containing between 35 and 60% w/w Tween 85. These data show that mixtures containing $\geqslant$ 35% w/w Tween 85 were capable of forming fine emulsions when sufficient mechanical shear was provided. Indeed the pure surfactant formed a fine emulsion when homogenized. Clearly the ability of such mixtures to 'self-emulsify' was a function of the amount of agitation provided. Strong forces of shear were required to disperse mixtures containing > 45% w/w Tween 85 probably due to the formation of viscous liquid crystalline structures at the droplet–water interface. The above behaviour was significantly different to that of mixtures containing 5 and 10% w/w Tween 85 which were not capable of forming fine emulsions even under conditions of high shear.

Miglyol 840, an oil of similar polarity to Miglyol 812, combined with Tween 85 to form similar self-emulsifying systems. The emulsification time was at a minimum when the proportion of Tween 85 in the self-emulsifying mixture was 35% w/w (Fig. 8). The particle size minimum occurred at 25% w/w Tween 85 (Fig. 9). Emulsions formed by mixtures containing less than 20% or more than 45% w/w Tween 85 were

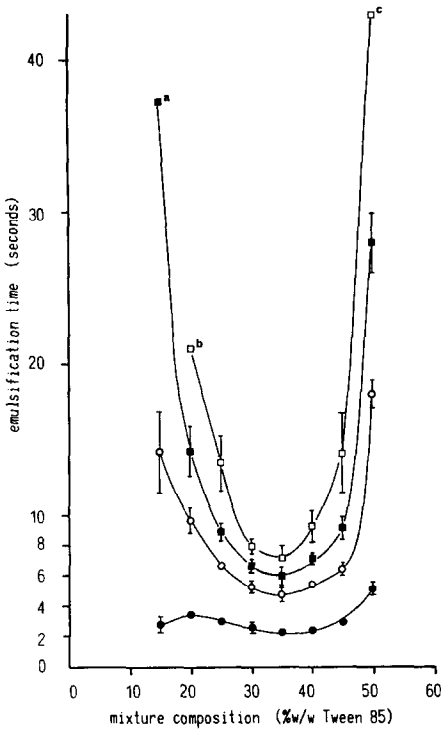

Fig. 8. Self-emulsification times of Miglyol 840/Tween 85 mixtures in distilled water at 25°C. (Mean ± S.D., n = 5). ● = t_0; ○ = t_{50}; ■ = t_{75}; □ = t_{90}. (a: S.D. = 11.4; b: S.D. = 3.8, c: S.D. = 4.0.)

poor. In summary, as with Miglyol 812 systems, rapid emulsification of Miglyol 840–Tween 85 systems was associated with the production of finely dispersed emulsions although the two optima did not occur at a coincident mixture composition. Fig. 8 shows that plots of each emulsification time (t_{50}, t_{75} and t_{90}) against mixture composition had the same general shape. This indicates that increases or decreases in the rate of emulsification were reflected in the whole plot of I_{Rel} against time. The standard deviations of emulsification times were lower (as a percentage of the mean) when emulsification took place rapidly, emphasizing the reproducible nature of self-emulsification.

Several other oils were mixed with Tween 85 to assess their ability to form self-emulsifying mixtures. In combination with Tween 85 most other oils were unable to form self-emulsifying mixtures. For example, mixtures of Tween 85 with a less polar oil, liquid paraffin or with a more polar oil, oleic acid formed very poor emulsions whatever the mixture compositions. Such emulsions were so poor that it was not possible to detect any scattered light using the nephelometer at the normal sensitivity level and the mean particle sizes of the emulsions were always out of the range covered by the Nano-Sizer. An oil closer in polarity to the Miglyols, glycerol trioleate, produced emulsions which were poor but not as poor as those formed with either liquid paraffin or oleic acid. These results emphasized the sensitive nature of

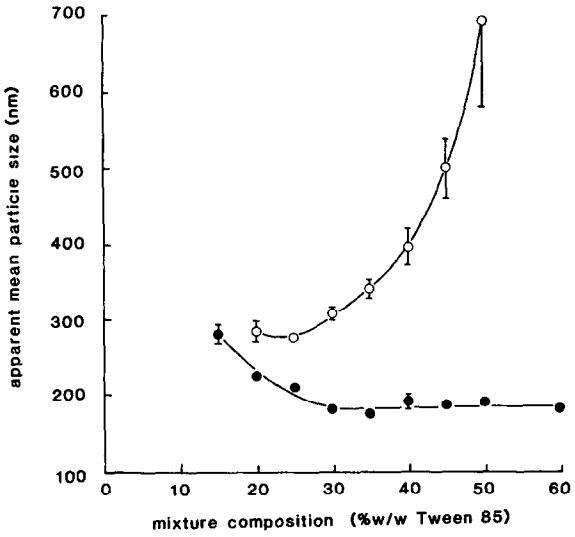

Fig. 9. Apparent mean particle size of self-emulsified and homogenized emulsions of Miglyol 840/Tween 85 mixtures in distilled water at 25°C (measured using a Coulter Nano-Sizer. Mean ± S.D. n = 3). ○ = self-emulsified systems; ● = homogenized systems.

self-emulsification and indicated that the chemical structure and hydrophile–lipophile balance of the surfactant required is likely to be highly specific for each oil.

Conclusions

The gentle conditions of agitation provided within the self-emulsification cell made the identification of useful self-emulsifying systems straightforward. Most oil–surfactant mixtures formed emulsions which scattered light weakly and, when examined by microscopy, were shown to consist of large particles (10–100 μm). In contrast self-emulsifying mixtures produced fine dispersions (< 1 μm) rapidly and in reproducible time. The Coulter Nano-Sizer provided a quick, non-invasive technique for comparing the mean particle sizes of resultant emulsions but was inappropriate for sizing all but genuine self-emulsifying systems. It is concluded that for comparison of self-emulsifying systems it is necessary to design a cell which provides reproducible conditions of agitation but that, once this has been achieved, assessment of particle size is more important than comparison of emulsification rate. The use of a nephelometer is useful to establish when dispersion has reached an equilibrium.

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