

# An investigation into the mechanisms of self-emulsification using particle size analysis and low frequency dielectric spectroscopy

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## Abstract

A series of mixtures comprising Imwitor 742 and Tween 80 have been prepared and their self-emulsifying properties studied using a method of visual examination. The particle size distributions of emulsions prepared from these mixtures at 25°C, 37°C in water and 37°C in 0.1 M HCl have been measured. A marked decrease in mean particle size was observed for 30 and 40% Imwitor 742/Tween 80 mixtures at 25°C with a decrease in particle size also being noted for the majority of Imwitor 742/Tween 80 compositions at higher temperatures. Low frequency dielectric spectroscopy was performed on the pure components and on binary systems to which water had been added to make 50% v/v mixtures. Evidence was shown for the formation of liquid crystalline phases at concentrations corresponding to those shown to be efficient self-emulsifying systems. The study therefore suggests that self-emulsification may be associated with liquid crystal formation and that low frequency dielectric spectroscopy may be of considerable use in understanding the factors leading to self-emulsification.

**Keywords:** Emulsion; Self-emulsifying system; Dielectric; Particle size; Tween; Glyceride; Imwitor

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## 1. Introduction

Self-emulsifying systems are a useful means of improving the bioavailability of poorly water soluble drugs (Lin et al., 1991; Charman et al., 1992; Craig, 1993). These dosage forms comprise a mixture of an oil and surfactant which, for reasons not yet fully understood, form an emulsion with little or no energy input when added to water. This would theoretically confer a considerable

advantage when formulating drugs, as such a mixture may form an emulsion in the stomach, thus presenting an incorporated drug to the GI tract in an emulsified form with a correspondingly high surface area for dissolution. While such systems have been reported to improve the bioavailability of drugs, notably cyclosporin (Ueda et al., 1984; Grevel et al., 1986; Tarr and Yalkowsky, 1989), the triglyceride component of the emulsions will be subject to enzymatic degradation by pancreatic lipase, hence it is not yet clear whether the improvements in bioavailability are a function of the self-emulsification process per se or whether incorporation into the oil is

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resulting in the drug being absorbed into the lymphatic system along with the glyceride component of the emulsions, as has been shown for a number of drugs in oil-based dosage forms (Armstrong and James, 1980). However, Tarr and Yalkowsky (1989) have shown that the particle size of the emulsion droplets has an effect on the bioavailability, hence whatever the mechanism involved, the self-emulsifying process is in itself of relevance to drug absorption.

The process by which self-emulsification takes place is not yet understood. The thermodynamic treatment of conventional emulsion formation has been described by Reiss (1975), assuming a simple two phase system. In this simplified case, the free energy of formation will be a direct function of the energy required to create a new surface between the two phases, hence

$$\Delta G = \sum_i N_i 4\pi r_i^2 \sigma \quad (1)$$

where  $\Delta G$  is the free energy associated with the process (ignoring the free energy of mixing),  $N$  denotes the number of droplets of radius  $r$  and  $\sigma$  is the interfacial energy. The two phases will tend to separate over a period of time in order to reduce the interfacial area between the two phases and hence to reduce the free energy of the system. Conventional emulsifying agents such as surfactants form a layer around the emulsion particles and hence reduce the interfacial energy, as well as providing a barrier to coalescence. In all these cases, however, the separation of the phases is merely being delayed, as thermodynamically these emulsions are still unstable.

In the case of self-emulsifying systems, the free energy required to form the emulsion is either very low and positive or actually negative (i.e., the formation is thermodynamically spontaneous). Work by Groves and Galindez (1976) and Wakerly et al. (1986) has suggested that a liquid crystalline phase forms between the oil/surfactant and water phases which effectively swells, thereby allowing 'spontaneous' formation of an interface between the oil droplets and the water. This may explain the high specificity of the proportions of oil and surfactant required for self-emulsification (Pouton, 1985), as the formation of

the liquid crystalline phase may be expected to be highly dependent on the proportions of oil, surfactant and water present.

In this study, the relationship between the composition of the oil/surfactant mixture and the emulsification process will be explored. Comparatively little work has been performed on studying the properties of the oil-surfactant-water liquid crystal gels themselves and relating that behaviour to the emulsification properties. These systems will be studied using low frequency dielectric spectroscopy and the structure of the gels related to their emulsification behaviour. The principles of low frequency dielectric spectroscopy have been outlined in a previous study on self-emulsifying systems (Craig et al., 1993a) as well as a number of other studies (Binns et al., 1992; Craig, 1992; Craig et al., 1993b). The method involves applying an alternating electric field to a sample over a frequency range of  $10^5$ – $10^{-2}$  Hz. The sample response may be analyzed in terms of the energy stored at any particular frequency (measured as the capacitance,  $C$ ) and the energy lost (measured as the dielectric loss  $G/\omega$ , where  $G$  is the conductance and  $\omega$  represents the angular frequency). By measuring these two parameters over the above frequency range it is possible to derive a spectrum from which information on the structure and behaviour of the sample may be obtained.

## 2. Materials and methods

### 2.1. Materials and visual examination

Emulsions were prepared from mixtures of Imwitor 742, a mixture of mono- and diglycerides of capric and caprylic acids (Huls, Germany) and Tween 80 (ICI, Macclesfield). 40 g samples were prepared containing 0–100% w/w Imwitor. The emulsifying properties were assessed using a visual test based on the CIPAC test (1973), whereby 0.6 ml of the mixtures were added to a beaker containing 400 ml water at room temperature (21°C) and the progress of the oil/surfactant droplets observed, particularly with a view to their tendency to emulsify 'spontaneously'. Sam-

ples were also agitated gently and the ease of emulsification noted. All studies were repeated at least once, with very similar observations being made between repeats.

### 2.2. Particle size analysis

0.5 ml of each mixture was introduced into a 1 l dissolution bath (USP) and stirred using a paddle speed of 70 rpm. Mixtures were introduced such that the tip was just below the surface of the water and the emulsions prepared in water at 25 and 37°C and also in 0.1 M HCl at 37°C. Particle size analysis was performed after 10 min stirring using a Malvern 2600 (Malvern Instruments Ltd, Malvern). This protocol was adopted in order to maximise the reproducibility of the particle size data. All measurements were repeated three times with coefficients of variation within 5%. The results are expressed in terms of the median ( $D_{50}$ ) value and the span, which is calculated from the  $D_{90}-D_{10}$  values divided by the median, where the  $D$  value refers to the % undersize.

### 2.3. Dielectric measurements

Measurements were performed using a Dielectric Spectrometer (Dielectrics Instrumentation Ltd, Worcs.), using a cell containing platinum electrodes of area 0.5 cm<sup>2</sup> and separation distance 1 mm, as described in a previous study (Craig et al., 1993a). An alternating signal (0.1 V r.m.s.) was applied to the sample over a frequency range of 10<sup>5</sup>–10<sup>-2</sup> Hz. The Tween 80 and Imwitor 742 were measured alone, followed by mixtures to which an equivalent volume of water had been added. At least three measurements were made at each frequency for each sample, yielding a maximum coefficient of variation of 3%. Duplicate runs yielded superimposable spectra.

## 3. Results and discussion

### 3.1. Visual examination

The results from the visual examination tests are given in Table 1. The tendency to form emul-

Table 1  
Visual assessment of emulsification for Imwitor 742/Tween 80 mixtures

Composition (% w/w Imwitor 742)	Ease of emulsification	Comments
0	bad	no emulsification seen even after gentle agitation. Droplets settled on the bottom of beaker
10	bad	no emulsification seen, although droplets broke up to form a layer at the bottom of the beaker
20	bad	no emulsification seen, but droplets spread at the bottom of the beaker to a larger extent than above. Some small droplets at top of beaker. On gentle agitation, droplets spread but no emulsion formed
30	good	droplets spread in beaker and formed emulsion on gentle agitation.
40	good	as in 30% mixture
50	good	as in 30% mixture
60	moderate	droplets formed layer on top of the beaker. Gentle stirring led to droplet emulsification and further spread.
70	good	formed emulsion on gentle agitation.
80	moderate	droplets formed layer on top of beaker which spread on agitation
90	moderate	as in 80% mixture
100	bad	droplets occupied top layer of water and no emulsion formed on agitation

sions appeared to be highly dependent on composition. The samples containing high proportions of Tween 80 formed droplets which rested at the bottom of the beaker. As Tween 80 is soluble in water, it is reasonable to assume that eventually a large proportion of this material would have dissolved. At 30–50% w/w and 70% Imwitor 742, a marked improvement in emulsifying properties was observed which was not seen at the intermediate concentration. At higher concentrations of Imwitor 742, the system formed an oily layer on

top of the water which showed only moderate emulsification properties. Clearly, the test is qualitative and as such is subject to only limited interpretation, particularly as the test gives no indication as to the quality of the emulsion but only to the ease of dispersion. However, such assessment is useful in establishing the concentrations which may be expected to exhibit anomalous behaviour in the other, more quantitative tests.

### 3.2. Particle size analysis

The results for the particle size analysis are shown in Table 2. The particle size data show that at 25°C in water, the oil/water mixtures form emulsions with a wide range of median particle sizes and spans. The Tween 80 alone shows multiple peaks and hence a comparatively wide span, indicating that it is not fully dissolving in the water under the conditions used for the study. The 10% Imwitor 742 systems also showed multiple peaks, although the median size was considerably larger. On increasing the concentration of Imwitor 742, a marked drop in median size was seen for the 30% w/w systems which extended through to the 40% w/w systems, after which the particle size increased again to values similar to those found for the lower concentra-

tions. The 30 and 40% Imwitor 742 systems also showed multiple peaks and there was no reduction in the span value for these systems.

The systems studied at 37°C in water showed a very different pattern, with the smaller size range seen at 30 and 40% w/w Imwitor 742 at 25°C noted at almost every concentration. When the systems were studied at 37°C in 0.1 M HCl, a similar trend to that seen for the systems in water was observed. The results therefore indicate that the self-emulsification process is, in this case, extremely sensitive to temperature, while a smaller set of changes were observed on changing the pH of the medium at 37°C.

Comparison of the particle size data obtained at 25°C with the visual observations shows that the good emulsification properties seen for 30 and 40% Imwitor 742 were reflected by the comparatively low particle size for the low temperature study. However, the 50 and 70% w/w systems did not show a decrease in particle size, despite demonstrating good spontaneity in the visual assessment. This could be a reflection of the fact that the visual test was a measure of the apparent spontaneity of emulsion formation, rather than a measure of the quality of the emulsion so formed. The discrepancy could also be due to the differences in temperature and in the way in which the samples were introduced to water in the two studies.

Table 2

Particle size data for Imwitor 742/Tween 80 self-emulsifying systems in a range of media

Composition (% Imwitor 742)	Water (25°C)		Water (37°C)		0.1 M HCl (37°C)	
	$D_{50}$ ( $\mu\text{m}$ )	Span	$D_{50}$ ( $\mu\text{m}$ )	Span	$D_{50}$ ( $\mu\text{m}$ )	Span
0	21.5	2.53	68.5	1.25	24.8	1.43
10	74.7	1.00	67.7	1.93	17.5	1.33
20	69.5	0.98	8.6	1.40	7.2	1.57
25	58.0	1.43	17.4	1.27	7.3	3.13
27	53.1	8.40	8.1	1.80	9.3	1.30
30	7.2	4.67	6.3	4.97	3.3	1.70
40	9.9	7.55	8.1	2.27	14.6	1.37
50	50.3	1.50	7.1	1.93	13.6	2.37
60	59.0	1.30	13.6	2.45	9.5	1.67
70	79.4	0.50	11.1	3.07	11.5	2.47
80	63.4	2.30	9.5	2.40	11.4	3.30
90	72.7	1.30	6.4	4.00	18.6	4.30
100	73.5	0.20	15.8	2.53	13.0	2.33

### 3.3. Dielectric analysis

Previous studies (Craig et al., 1993a) have indicated that dielectric analysis may be of use in studying the behaviour of the oil/surfactant mixtures themselves, notably in terms of the effect of added drugs. Given the data discussed above, it is clear that at 25°C the behaviour of the mixtures is highly dependent on composition. Assuming that the formation mechanism suggested previously (Groves and Galindez, 1976; Wakerly et al., 1986) is correct, this concentration dependence implies that the tendency to form liquid crystalline phases may be greatest at 30–40% w/w Imwitor 742. The dielectric responses of the various mixtures were therefore examined in order to investigate the possibility of liquid crystal formation using

oil/surfactant mixtures to which an equivalent volume of water had been added. It should be noted that high concentrations of Tween 80 in water may form liquid crystals in any case (Nixon and Chawla, 1969), hence in terms of the relationship between self-emulsification and liquid crystal formation, the specificity of the oil-surfactant ratio for emulsification noted by previous authors (e.g., Pouton, 1985) may reflect not simply the presence or absence of liquid crystals but the formation of specific liquid crystalline structures which facilitate the emulsification process.

The dielectric responses of the Tween 80 and the Imwitor 742 are shown in Fig. 1. These spectra represent relatively simple dielectric systems containing three distinct regions. The high frequency capacitance shows a frequency independent region which corresponds to the dielectric constant (relative permittivity,  $\epsilon_r$ ) of the sample. Second, the dielectric loss shows a region corresponding to d.c. conductivity at higher frequencies ( $> 1$  Hz). This may be concluded from the observation that the slope of the logarithmic dielectric loss ( $G/\omega$ ) against frequency is  $-1$ , indicating that  $G$  is constant in this region. Finally, the low frequency response ( $< 1$  Hz) represents the behaviour of an electrode layer. These layers have been described in detail in previous publications (Hill and Pickup, 1985; Binns et al., 1992) and may be used as a means of assessing the

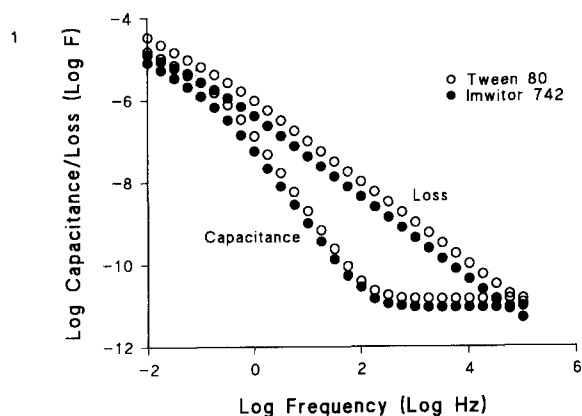


Fig. 1. Dielectric response of Tween 80 and Imwitor 742 at 25°C.

Table 3

Dielectric data for Imwitor 742/Tween 80 systems (25°C)

Composition	Dielectric loss ( $10^2$ Hz) (F)	Specific conductivity at $10^2$ Hz (Mho)	Slope of low frequency capacitance ( $10^{-1}$ – $10^{-2}$ Hz)
Pure materials			
Imwitor 742	$4.327 \times 10^{-9}$	$5.438 \times 10^{-7}$	-0.815
Tween 80	$1.141 \times 10^{-8}$	$1.434 \times 10^{-6}$	-0.721
Mixtures with water (50% v/v)			
Composition of oil/surfactant component of mixture (% w/w Imwitor 742)			
0	$1.550 \times 10^{-6}$	$4.869 \times 10^{-4}$	-0.461
20	$1.567 \times 10^{-6}$	$4.922 \times 10^{-4}$	-0.476
30	$1.253 \times 10^{-7}$	$1.575 \times 10^{-5}$	-0.636
40	$1.146 \times 10^{-6}$	$1.440 \times 10^{-4}$	-0.461
50	$1.276 \times 10^{-6}$	$1.604 \times 10^{-4}$	-0.479
60	$3.275 \times 10^{-6}$	$4.116 \times 10^{-4}$	-0.467
70	$2.256 \times 10^{-7}$	$2.828 \times 10^{-5}$	-0.504
80	$2.105 \times 10^{-6}$	$2.646 \times 10^{-4}$	-0.395
100	$3.249 \times 10^{-6}$	$4.084 \times 10^{-4}$	-0.320

behaviour of the constituent molecules of a system, as the layers are composed of adsorbed molecules of one or more components. The ability of these layers to block charge is given by the logarithmic slope of the capacitance in the low frequency region, with a value close to 0 indicating a complete block of charge movement through the layer. Values closer to  $-1$  indicate 'leakiness' of the blocking layer to moving charges.

Representative values of the dielectric loss and conductivity in the high frequency d.c. region and the capacitance slope in the low frequency barrier layer region are shown for the various systems in Table 3. The responses of both the oil and surfactant systems are similar and show both materials to exhibit a relatively high conductivity. The response of the Tween 80/water system is shown in Fig. 2 and Table 3 in comparison to pure Tween 80. The high frequency dielectric loss has increased, as expected due to the presence of the more highly conductive water, but the nature of the low frequency response has also altered. This implies that the nature of the electrode layer has changed. The slope of the low frequency capacitance in the frequency range  $10^{-1}$ – $10^{-2}$  Hz is  $-0.461$  for the aqueous Tween 80 systems,

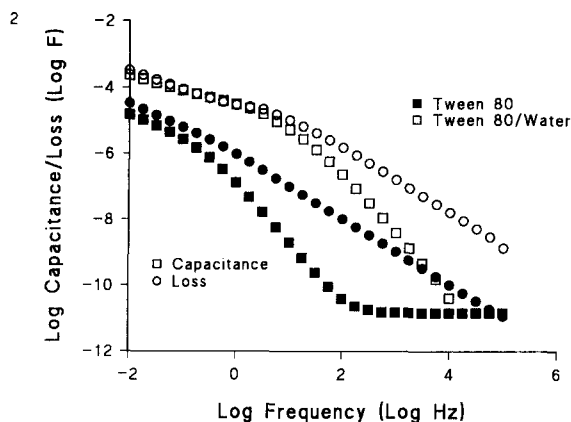


Fig. 2. Dielectric response of Tween 80 alone and as a 50% v/v aqueous system at 25°C.

as opposed to  $-0.721$  for Tween 80 alone. This implies that a much less 'leaky' layer has been established which is more effective at blocking charge transport than was found for the Tween 80 alone, possibly reflecting the establishment of a gel layer on the electrodes. A similar trend is seen for the 20% w/w Imwitor 742/Tween 80 systems, as shown in Fig. 3. However, for the 30% w/w systems, where a reduction in the particle size of the corresponding emulsions was noted, a marked change in spectral shape was seen. There are essentially three differences between the 20 and 30% spectra, all of which indicate changes in the structure of the system which may not be explained simply by a change in proportion of Imwitor 742/Tween 80. First, the low frequency response ( $<1$  Hz) shows a marked change between the two systems, with capacitance slopes of  $-0.476$  and  $-0.636$  for the 20 and 30% systems respectively. As discussed above, this slope represents the ease with which charge may penetrate through the barrier layer, this in turn being a reflection of the packing of molecules into the layer. The change in slope reflects an increased leakiness for the barrier layer of the 30% system.

At higher frequencies, (1–1000 Hz), the dielectric loss, and hence conductivity of the system has decreased considerably, as indicated in Table 3. This means that either the number of charges present in the system has become reduced in

absolute terms, or else the mobility of those charges has decreased. As there is no reason to expect a reduction in the absolute numbers of charges within this system, it may be concluded that those charges are less mobile at this particular composition. Thirdly, at higher frequencies ( $10^4$ – $10^5$  Hz), a further process is seen which, at least over this frequency range, was absent for the 20% Imwitor 742 system. Previous studies (Ramdeen et al., 1984) have ascribed such effects to charge-hopping responses, whereby instead of a charged species moving from one electrodes to the other effectively freely, charges move by 'hopping' between specific sites in the sample. The presence of such sites implies discrete regions within the sample, between which the charges may move.

These differences all indicate that liquid crystalline phases are forming in the 30% w/w system. The lowest frequency response indicates that the diffusion layer of adsorbed material has now been disrupted to such an extent that there is little barrier layer present. Given the structure of the barrier layer observed for the Tween 80/water systems alone, it is logical to suggest that the formation of the liquid crystalline gel has effectively removed the Tween 80 molecules which were previously comprising the barrier layer. This is supported by the decrease in conductivity, again implying that the mobility of the charges within

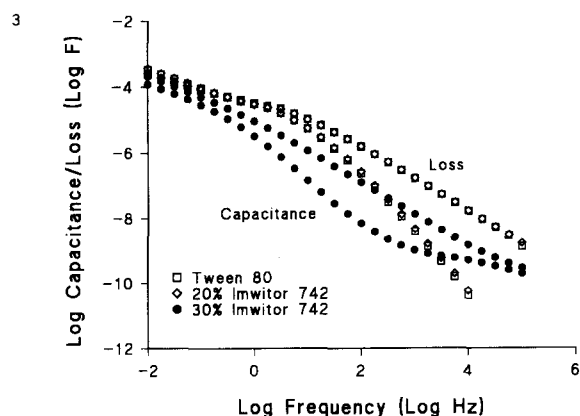


Fig. 3. Dielectric response of aqueous Tween 80, 20% w/w Imwitor 742 and 30% Imwitor 742 at 25°C.

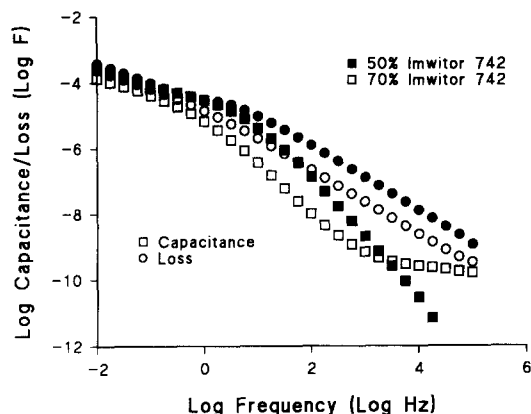


Fig. 4. Dielectric response of aqueous 50% Imwitor 742 and 70% Imwitor 742 at 25°C.

the system has decreased considerably. The highest frequency response provides further evidence that the molecules are present in an ordered structure which allows only hindered movement of charge through the different regions. The dielectric technique has therefore afforded three pieces of evidence to suggest that in the 30% systems, a liquid crystal phase has been formed.

On increasing the proportion of Imwitor to 40%, the response returned to that seen for the 20% system. A similar response was seen for the 50% systems. However, at 70% Imwitor, the response again showed evidence for structuring, as shown in Fig. 4. While this concentration did not produce the dramatic particle size reduction seen for the 30% systems, the visual assessment did indicate that this system showed good emulsification properties. The 100% Imwitor system showed a well defined barrier layer (Fig. 1) but did not show any evidence for liquid crystal formation. There is therefore a reasonable, although not total, correlation between the results of the dielectric study and those of the visual assessment and particle size analysis. Furthermore, while the technique does not provide unequivocal evidence for the absence of liquid crystals in the poorly-emulsifying mixtures, it strongly indicates that the 30 and 70% samples are forming structures which are absent in the other mixtures under study.

#### 4. Conclusions

The study has investigated the self-emulsifying properties of a series of Tween 80/Imwitor 742 systems, both by visual assessment and particle size analysis. The two techniques gave largely complementary results and confirmed previous observations (e.g., Pouton, 1985) that the emulsion formation process may be highly dependent on the composition of the oil-surfactant mixture. Furthermore, the study showed the formation process to be highly dependent on temperature, a conclusion which has also been noted for Tween 80/Miglyol systems by Wakerly et al. (1986).

The dielectric studies provide evidence that the formation of the emulsions may be associated with liquid crystal formation, although the relationship is clearly complex and further studies need to be performed in order to clarify the processes involved. While it is appreciated that structuring of some description may be occurring in other, or indeed all the systems, the responses for 30 and 70% w/w mixtures clearly indicate that these concentrations exhibit anomalous behaviour compared to the others. This technique may be of considerable value in examining liquid crystal formation in general as it is non-invasive and may examine concentrated systems, hence there is no requirement for dilution or other manipulations which may alter the structure of the gel phase. Furthermore, the technique may provide a quantitative assessment of parameters associated with the liquid crystal formation process, as not only the individual points but the spectral shape may be described numerically. This is in contrast to standard microscopic techniques, which provide evidence which is not only qualitative but is also frequently inconclusive and operator dependent. While more work is required to relate the dielectric spectra specifically to the structures present, this investigation clearly indicates that low frequency dielectric spectroscopy has a role to play as a novel means of studying liquid crystal formation.

There are, however, a number of discrepancies associated with the emulsification behaviour of the systems under study. In particular, the concentrations corresponding to the best emulsifica-

tion properties, as assessed visually, do not correspond exactly with the concentrations showing the greatest reduction in particle size in relation to other compositions. This is seen particularly for the 70% w/w systems, whereby good spontaneity of emulsification is not matched by a reduction in particle size. Furthermore, this concentration showed evidence for liquid crystal formation in water using dielectric analysis, hence in this respect there is greater agreement between the dielectric studies and the visual assessment than with the particle size analysis. The mechanisms behind this discrepancy are not yet clear, although the current paucity of information available regarding the mechanisms of emulsification for these systems renders any further interpretation difficult. Indeed, the study has highlighted the need for a more fundamental examination of the emulsification process, especially as the relationship between the spontaneity of emulsification, the particle size of the formed emulsion and the propensity of the oil-surfactant mixture to form liquid crystals is clearly complex. However, the investigation has allowed an insight into the nature of this relationship and suggests that with further studies it should be possible to develop a deeper understanding of the emulsification process, thus considerably enhancing the predictability of the behaviour of self-emulsifying systems.

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