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An investigation into the physico-chemical properties of self-emulsifying systems using low frequency dielectric spectroscopy, surface tension measurements and particle size analysis

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Summary

The structure and behaviour of self-emulsifying drug delivery systems (SEDDS) containing Labrafil M2125 CS and Tween 80 have been examined and the effects of changing the formulation via the addition of a non-polar model drug (L-365,260) investigated. Low frequency dielectric spectroscopy (LFDS) was used to examine the individual components in order to investigate the effects of drug inclusion. The presence of the drug resulted in a decrease in the dielectric response of the Labrafil M2125 CS, Tween 80 and the oil-surfactant vehicles. The surface tension of the emulsions decreased on addition of the drug, while particle size analysis showed that the emulsions containing no drug and 2% w/v drug had a bimodal distribution and the emulsions containing 6% w/v drug were unimodal. It was found that the bimodal distribution changed over a period of 14 h, with a decrease in modal value of the larger distribution peak and, for samples containing no drug, an increase in the proportion of droplets in the lower size distribution. The results therefore indicate that the drug interacts with one or more components of the self-emulsifying system, leading to a change in droplet size distribution which varies as a function of drug concentration.

Introduction

Self-emulsifying systems have been described as mixtures of oil and surfactant which emulsify in water under conditions of gentle agitation (Pouton, 1985). These systems may be used as drug delivery vehicles by incorporating poorly water-soluble drugs in the oil-surfactant mixture which may then be taken orally, for example, in soft gelatin capsules. An emulsion forms in the GI tract, yielding a large surface area for releasing the dispersed drug, this process being energetically more favourable than the dissolution of the crystalline drug.

As the dissolution rate of poorly soluble substances is frequently the rate limiting step to absorption, formulation in this manner may result

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in improved drug bioavailability (Lin et al., 1991). These oil-surfactant-drug mixtures are known as self-emulsifying drug delivery systems (SEDDS). Although these systems have attracted considerable interest as potential dosage forms, neither the mechanism by which emulsification occurs nor the effect of added components such as drugs on the formation process are fully understood.

In the present study, the physico-chemical properties of the components of SEDDS, both with and without drug, have been examined using low frequency dielectric spectroscopy (LFDS). The surface tension and particle size of the corresponding emulsions have been assessed and their short-term stability examined. As LFDS is a comparitively new technique within the pharmaceutical sciences, a brief introduction to the principles of the method will be given.

Theory of Low Frequency Dielectric Spectroscopy

The application of an electric field to a sample will result in the polarisation of that material. When an alternating field is applied, the charges within the system will attempt to compensate for the changes in field direction by a number of mechanisms, including reorientation and charge-hopping. The overall effect will be the movement of charge within the sample, thus generating a polarisation current (P). At any frequency, the relationship between the polarisation and the applied field will be given by:

$$P(\omega) = \chi(\omega) \cdot E(\omega) \tag{1}$$

where the subscript (ω) denotes that the equation describes the relationship at frequency ω. The term χ refers to the susceptibility of the sample, which is a measure of the responsiveness of that material to an electric field. Under an alternating field, the term is complex due to the vectorial nature of the response, i.e., the relationship between the field and polarisation must be considered in terms of both the magnitude and the phase behaviour of the response, thus:

$$\chi^*(\chi) = \chi'(\omega) - i\chi''(\omega) \tag{2}$$

where i is the square root of -1 and χ' and χ'' represent the real and imaginary components of the susceptibility, respectively. These two components may be considered to represent the energy stored and lost from the system. However, the susceptibility of a sample is an intrinsic property of that material and may not be directly measured. Using a cell containing electrodes of area A and separation distance d, the response may be expressed in terms of the capacitance (C) and dielectric loss (G/ω, where G is the conductance) by:

$$C = \frac{\epsilon_0 A}{d} \cdot [\chi'(\omega) + \epsilon(\infty)] \tag{3}$$

and

$$G/\chi = \frac{\epsilon_0 A}{d} \cdot \chi''(\omega) \tag{4}$$

where ϵ_0 is the permittivity of free space and $\epsilon(\infty)$ denotes the permittivity at infinite frequency.

The conductivity (G) in Eqn 4 reflects the movement of charge due to reorientation of dipoles from one position to another (known as a.c. conductivity). In many systems, however, free charges exist which may move from one electrode to the other, thus generating a direct current ($G_{d.c.}$). This may be accounted for by including a d.c. term in Eqn 4, thus:

$$G/\omega = \frac{\epsilon_0 A}{d} \cdot \chi''(\omega) + G_{d.c.}/\omega \tag{5}$$

In systems in which d.c. conductivity predominates, examination of Eqn 4 shows that the dielectric loss will be inversely proportional to frequency.

The capacitance and dielectric loss therefore give an indication of the real and imaginary susceptibilities, respectively. As dielectric behaviour is related to the structure of a material, measurement of these two components over a range of frequencies yield spectra which are characteristic of the properties of that sample. Further details of the principles and uses of dielectric spec-

troscopy are available from a number of texts (e.g., Debye, 1940; Hill and Jonscher, 1983; Craig, 1992).

As dielectric phenomena occur over a wide range of frequencies, several methods are available for their measurement, the choice depending largely on the frequency range under examination. The present study concerns the use of low frequency dielectric analysis, whereby the frequency range under examination is between 10^5 and 10^{-2} Hz. In this spectral region, the response of aqueous disperse systems such as gels (Dissado et al., 1987; Rowe et al., 1988), emulsions (Hill et al., 1990) and liposome suspensions (Barker et al., 1989) represents two phases within the system: at high frequencies (greater than approx. 1 Hz) the response reflects the behaviour of the bulk (aqueous) phase, whereas at lower frequencies the response represents layers adsorbed onto the electrodes. It has been proposed that the low frequency response gives an indication of the structure of interfacial or other thin layers within the system (Hill and Pickup, 1985) and thus represents a method of simultaneously analysing different components within a formulation.

The interpretation of the low frequency spectra has been discussed in detail by Hill and Pickup (1985). The essential features of the analysis are summarised as follows:

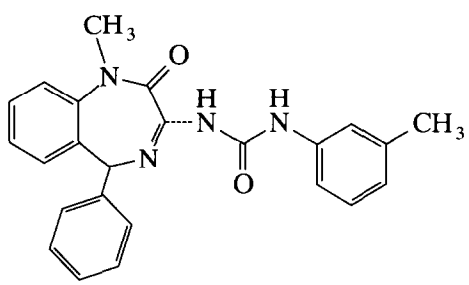
(1) The slope of the high frequency loss indicates the bulk conduction mechanism. The capacitance and loss are usually plotted against frequency on logarithmic scales. For d.c. conductance processes, the value of G is constant with frequency, hence on the above scales the slope of the loss (G/ω) against frequency will be -1. If the slope deviates from this value, it indicates that the conductance process is not d.c., for which charge may move freely from one electrode to another. Instead, charge may move via a charge-hopping process, whereby ions or electrons transfer between specific sites within the system.

(2) The slope of the low frequency capacitance (below approx. 1 Hz) is an indication of the effectiveness of the adsorbed layer to block charge movement. For a layer through which no charge may pass directly, the low frequency capacitance will be independent of frequency (i.e., the slope will be horizontal), while for systems through which charge may pass (i.e., the layer acts as a 'leaky' capacitor) the slope of the low frequency capacitance will be negative. By measuring the slope of the low frequency capacitance, it is therefore possible to assess the permeability of the surface layer to charge movement, from which information on the structure of the layer may be extrapolated. It is not always possible to measure the low frequency capacitance as this region of the spectra may not be seen within the frequency range of the equipment. However, it has been shown theoretically (Hill and Pickup, 1985) and experimentally (Binns et al., 1992) that the sum of the low and high frequency capacitance slopes is -2, hence the low frequency slope (indicating the structure of the electrode layer) may be estimated by measuring the slope of the capacitance at high frequencies.

Materials and Methods

Materials

The model drug used was L-365,260, a poorly water soluble benzodiazepine derivative with the structure given below



L-365,260

A series of oil-surfactant vehicles were prepared containing ethoxylated oleic linoleic glycerides (Labrafil M2125 CS, Gattefosse, Saint-Priest, France), polyoxyethylene (20) sorbitan mono-oleate (Tween 80, ICI Chemicals, Macclesfield), propylene glycol (K and K Greef Ltd, Croydon), water and L-365,260 according to the formula given below. The Labrafil M2125 CS, Tween 80 and propylene glycol were mixed to-

gether, followed by the drug and finally the water. This formulation was chosen on two criteria: the ability to form an emulsion on minimal agitation and the capacity to incorporate sufficient quantities of the drug in order to produce a viable dosage form. In addition, 2% w/v solutions of drug in Labrafil M2125 CS and Tween 80 alone were prepared.

Components	Sample 1	Sample 2	Sample 3
Labrafil M2125 CS	62%	60%	56%
Propylene glycol	3%	3%	3%
Tween 80	30%	30%	30%
Distilled Water	5%	5%	5%
L-365,260	0%	2%	6%

Dielectric measurements

Measurements were performed at 303 K using a low frequency dielectric spectrometer (Dielectric Instrumentation, Worcs). Approx. 3 ml of sample were placed in a PTFE pot and two stainless steel electrodes (area 0.5 cm^2, separation distance 1 mm) inserted into the liquid. A voltage of 0.1 V r.m.s. was generated by a frequency response analyser (FRA) and passed through the sample via an interface. The returning signal was analysed by the FRA and displayed in terms of the capacitance and dielectric loss. Each spectral point represents an average of three measurements and repeat studies showed good reproducibility.

Surface tension measurements

Emulsions from samples 1–3 were prepared by adding 0.5 ml of sample to 200 ml purified water and the system mixed in a standard manner using a magnetic stirrer. Surface tensions were measured using a DuNouy apparatus (Central Scientific Company, Chicago) at 20.5°C. This consists of a platinum ring with a circumference of 4 cm, which was brought in contact with the sample. The surface tension was measured as the force required to free the ring from the liquid surface. Measurements were repeated eight times.

Particle size analysis

Particle size analysis was performed using a Malvern Master Sizer (Malvern Instruments Ltd, Malvern), which has a particle size measurement range of 100–0.2 μm. The data were calculated from a volume size distribution. All studies were repeated, with good agreement being found between measurements.

Results and Discussion

Dielectric measurements

The dielectric response of Labrafil M2125 CS alone is shown in Fig. 1. It was not possible to measure the medium frequency range capacitance due to excessive noise. However, the spectra show that the oil has a measurable conductance, as given in Table 1. The conductance was d.c. in nature, as shown by the loss slope which was close to the theoretical value of -1, hence specific conductance values (κ) have been calculated via:

$$\kappa = \frac{dG}{A} \tag{6}$$

where d is the interelectrode distance, A represents the electrode area and G is the conductance of the sample. Measurements are given at 10^3 Hz, as the conductivity is frequency independent in this region and hence provides a

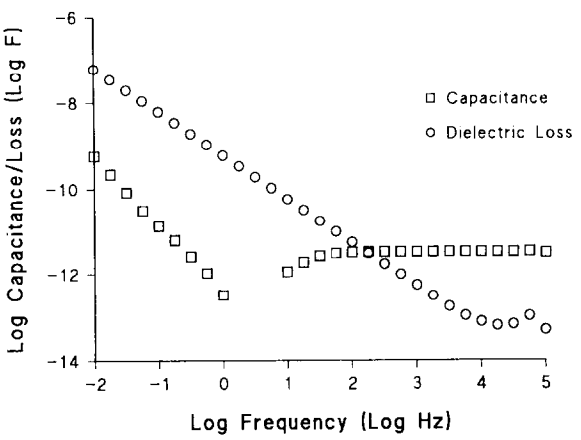


Fig. 1. Dielectric response of Labrafil M2125 CS.

TABLE 1

Characteristic parameters associated with the dielectric response of self-emulsifying systems

System	Specific conductance at 10^3 Hz (Ω^{-1} cm^{-1})	Slope of dielectric loss (10^4–10^2 Hz)	Slope of capacitance (10^1–10^0 Hz)
Labrafil M2125	9.300×10^{-10}	−0.97	–
Labrafil M2125 2% drug	8.988×10^{-10}	−0.99	–
Tween	7.556×10^{-7}	−1.00	−1.72
Tween 80 2% drug	5.806×10^{-7}	−1.01	−1.76
Sample 1	4.242×10^{-7}	−1.02	−1.81
Sample 2	2.472×10^{-7}	−1.02	−1.83
Sample 3	1.377×10^{-7}	−1.02	−1.81

reasonable comparison between samples. It is likely that the Labrafil M2125 CS contains components which are capable of carrying charge, possible candidates being the free fatty acids within the sample. However, the values of conductance given in Table 1 are comparitively low, as would be expected for a non-aqueous system. At low frequencies, a further mechanism is observed, indicated by the low frequency increase in capacitance. This may correspond to an adsorbed electrode layer of Labrafil M2125 CS molecules (Hill and Pickup, 1985). Addition of 2% drug caused a small decrease in the conductance, implying that the movement of charges through the system is impeded on addition of the drug.

The response of Tween 80 was of considerably greater magnitude than that of the Labrafil M2125 CS, as shown in Fig. 2. The spectrum is typical of

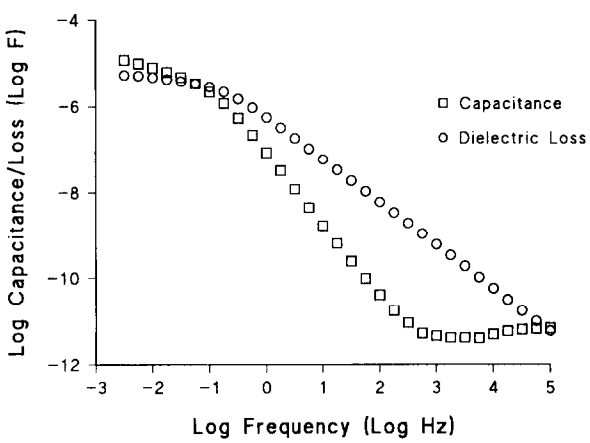


Fig. 2. Dielectric response of Tween 80.

the Maxwell-Wagner response described previously, whereby at high frequencies the behaviour is dominated by a bulk conduction mechanism (as shown by the slope value of approximately −1), while at lower frequencies a barrier layer is seen, again corresponding to an adsorbed layer at the electrodes. The slope of the high frequency capacitance (taken at 10^0–10^{-1} Hz to allow comparison) is −1.72, indicating that the low frequency capacitance slope is −0.28. The difference between this value and the theoretical value of 0 for a layer which completely blocks charge movement implies that the Tween 80 forms a loose adsorbed layer on the electrode surface, through which charge may pass reasonably easily. Addition of 2% w/v drug caused a decrease in conductance, as shown in Table 1, while the capacitance slope showed little change. This indicates that the movement of charge through the system is impeded, yet the structure of the adsorbed electrode layer remains essentially unchanged.

The responses of samples 1 and 3 are shown in Fig. 3. Again, the spectra are of the Maxwell-Wagner type, with a low frequency (< 0.1 Hz) response reflecting the presence of an adsorbed barrier layer and a high frequency response reflecting a bulk conductivity process. The magnitude of the conductance for sample 1 is lower than that of the Tween 80, but considerably higher than that of the Labrafil M2125 alone, as shown in Table 1. Indeed, the conductance of the vehicle is, in comparison to the value for the Labrafil M2125 CS alone, only marginally smaller than

that of the Tween 80, despite the proportion of surfactant present being small compared to that of the Labrafil M2125 CS. The similarity may be due to the presence of the water and propylene glycol, although the form in which these components exist within the mixture is not known. Earlier studies (Groves and Mustafa, 1974; Groves and De Galindez, 1976) have discussed the formation of liquid crystalline phases in SEDDS vehicles on addition of water, hence the results may reflect structuring within the system.

Table 1 and Fig. 3 show that the change in formulation causes a decrease in the conductance of the vehicle, despite the lower proportion of Labrafil M2125 CS present as the drug content increases. The effect may therefore be ascribed to the presence of the drug, particularly as a lowering of the conductance was also observed on addition of drug to the Tween 80 and Labrafil M2125 CS alone. However, the slope of the capacitance remains unchanged in the presence of drug. It may therefore be concluded that again the drug has a significant effect on the movement of charge through the system but does not affect the layer adsorbed onto the electrodes.

Surface tension measurements

While it is often possible to use the method of Girifalco and Good (1957) to estimate the interfacial energy of oil-water systems, the complexity of both the interface and the mechanism of formation renders this type of analysis inappropriate. In this case, therefore, the surface tensions of the formed emulsions have been measured in order to monitor the behaviour of the water-air interface. As air is a relatively hydrophobic medium, changes in the surface tension may be regarded as an indication of changes in the oil-water interfacial behaviour.

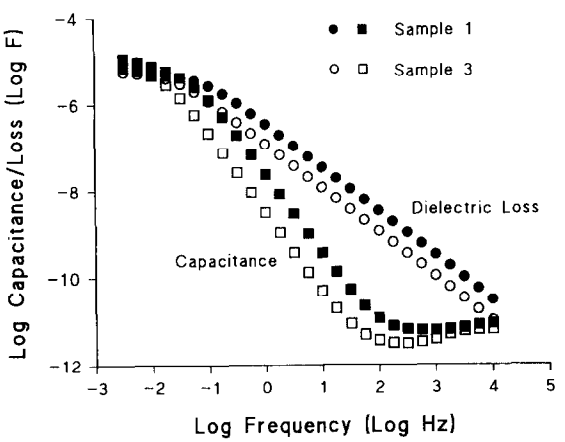


Fig. 3. Dielectric response of samples 1 and 3.

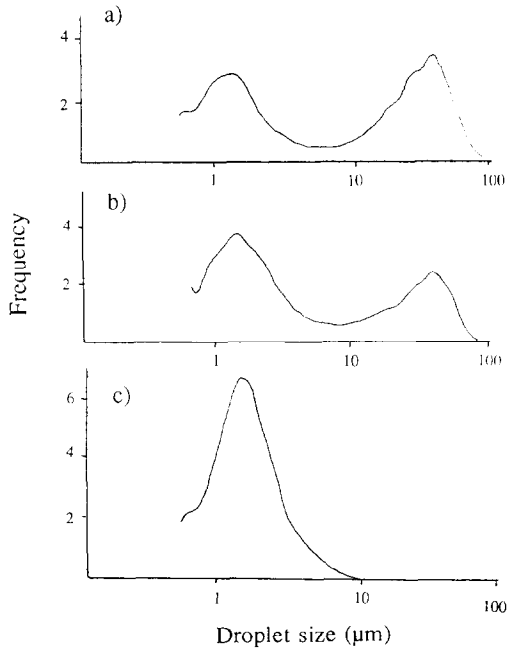


Fig. 4. Droplet size of emulsions prepared from (a) sample 1, (b) sample 2, (c) sample 3.

The surface tensions of emulsions formed from samples 1–3 were measured as 39.63 ($\pm$0.36) mN m^{-1}, 38.45 ($\pm$0.17) mN m^{-1} and 37.86 ($\pm$0.47) mN m^{-1}, respectively. These differences are significant ($p < 0.05$, $n = 9$) using a Student's t-test. Inclusion of the drug therefore results in a concentration-dependent decrease in the surface tension.

Particle size studies

The particle size distributions of the emulsions prepared from samples 1 and 2 were found to be bimodal, while the emulsions prepared from sample 3 were found to exhibit a single peak, as indicated in Fig. 4a–c. The modal particle sizes of the peaks are shown in Table 2 along with the

TABLE 2

Particle size data for self-emulsifying systems

System	Modal particle size (upper peak) (μm)	Modal particle size (lower peak) (μm)	% in lower distribution
Sample 1	35.7	1.19	49.7
Sample 2	35.3	1.59	68.2
Sample 3	–	1.44	100
Sample 1 (14 h)	16.7	1.14	59.8
Sample 2 (14 h)	16.3	1.34	77.3

frequency percentage in the lower distribution, calculated from cumulative frequency data (the droplet size corresponding to the minimum frequency value between the peaks was taken as the separation point between the two distributions). The proportion of droplets in the lower size range increased between samples 1 and 3, demonstrating that the change in formulation has a significant effect on the distribution of particle sizes.

Emulsions prepared from samples 1 and 2 were retested after storage under ambient conditions for 14 h. The results are shown in Fig. 5a and b and Table 2. In both cases, there was a marked decrease in particle size in that a greater proportion of particles were in the lower size distribution, implying that the larger droplets had broken down to form smaller ones. Furthermore, the mode of the higher peak decreased and the proportion of particles in the lower size distribution increased.

Conclusions

The physico-chemical properties of SEDDS have been assessed using LFDS, surface tension measurements and particle size analysis. Data have been presented which demonstrate firstly the usefulness of these techniques in examining the properties of SEDD systems and secondly the effects of changing the formulation on those properties. LFDS has been used to examine the constituents of the emulsions and has been shown to give characteristic spectra for the oil, surfactant and vehicles. The presence of the drug decreased the charge carrying properties of all three samples, although the adsorbed electrode layer seen for the Tween 80 and vehicles remained unaltered. As the charge carrying process is likely to be due to small molecules within the system such as free fatty acids or trace impurities rather than the constituent surfactant or oil molecules, these results may directly reflect the behaviour of

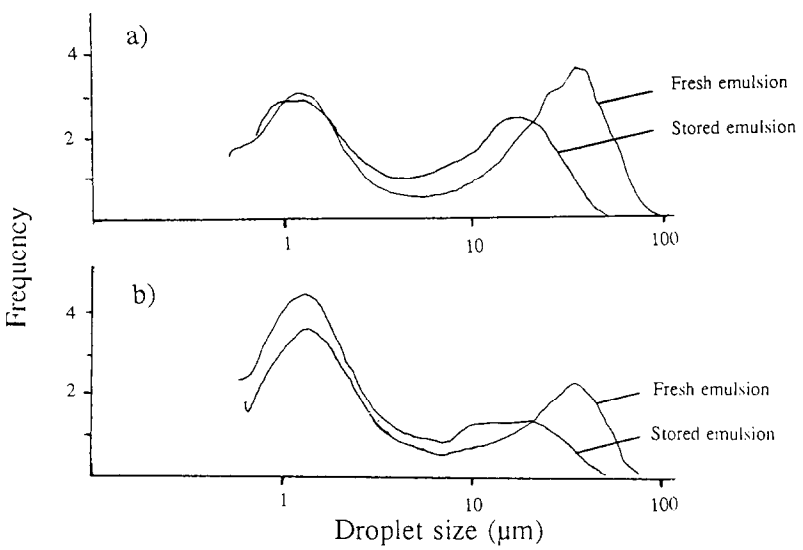


Fig. 5. Droplet size of emulsions prepared from (a) sample 1 and (b) sample 2 after 14 h.

these smaller molecules, rather than the larger molecules within the system which are unlikely to appreciably carry charge. It is possible that the drug is blocking charge movement through the system by physical obstruction, as has been suggested for diclofenac sodium in alginate gels (Binns et al., 1992), or alternatively the drug could be directly complexing with the lower molecular weight components. While more work is required in order to clarify these processes, the study demonstrates the potential of dielectric analysis in the study of non-aqueous liquids.

The surface tension of the emulsions decreased in the presence of the drug, while particle size analysis showed a decrease in droplet size of the subsequent emulsions on addition of the drug. It is therefore reasonable to assume that the decrease in surface tension resulted in a similar decrease in vehicle/water interfacial energy. This in turn may be expected to result in a decrease in overall particle size, as was indeed observed. The distribution of droplet sizes was also dependent on the formulation, although the mechanism reponsible for this effect is as yet unclear. Pouton (1985) has suggested that relatively small changes in the oil-surfactant ratio may effect the size distribution of the formed emulsions, hence the observed effect may to some extent be a function of the changes in the proportion of Labrafil M2125 CS to Tween 80 as well as the interaction between the drug and excipients suggested by the dielectric studies.

A lowering in droplet size and changes in distribution were observed on storing emulsions from samples 1 and 2. This size decrease may be a function of the free energy of formation of self-emulsifying systems, which is either negative or has a very small positive value, allowing formation to occur with only a minimal energy input. If the free energy of formation is indeed negative, then particle size reduction will occur spontaneously, while the droplet size increase normally associated with stored emulsions will be thermodynamically unfavoured. It is therefore possible that the results presented here are evidence for a negative free energy of formation for these systems. The decrease in droplet diameter could have physiological significance, as drug release and hence absorption may be related to the size of the droplets.

The study has investigated the properties of a relatively complex SEDDs, hence it will be necessary to examine the behaviour of the individual components in more detail before it is possible to offer a more fundamental explanation of the observed effects. However, the study demonstrates the problems that may be associated with the use of SEDDS in a practical situation. Not only must the solubility of the drug be considered when choosing a vehicle, perhaps necessitating the use of additional components such as propylene glycol or water, but the effect that the drug may have on the emulsification process must also be accounted for. The study has also demonstrated the use of dielectric spectroscopy in the investigation of SEDD systems, as it has shown changes in the bulk properties of the various systems on addition of the drug which may be related to the differences in droplet size distribution noted for the formed emulsions. Again, it will be useful to examine simpler systems using the technique, particularly in terms of studying the phase behaviour of oil-surfactant-wate systems, as it may be possible to gain information on the structure of the liquid crystal phases which are believed to be present at the oil-water interface in the formed emulsions (Groves and Mustafa, 1974; Groves and de Galindez, 1976), the technique may allow a greater understanding of the mechanisms of self-emulsification which in turn will allow a more rational approach to SEDDS formulation.

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