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The emulsification and solubilisation properties of polyglycolysed oils in self-emulsifying formulations

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Abstract

Self-emulsifying drug delivery systems (SEDDS), whereby drugs are dispersed in an oil–surfactant mix that emulsifies on contact with water, represent a highly promising approach for enhancing oral bioavailability. However, the choice of formulation is, at present, largely empirical both in terms of the composition dependence of the emulsification process and the solubilisation of the drug in the initial oil–surfactant mixture. In this investigation, a range of chemically related self-emulsifying systems have been studied, based on the Labrafil family of polyglycolysed oils, using Tween 80 and Tween 20 as surfactants. The ease of emulsification, the particle size distribution and the appearance of the emulsion droplets were studied as a function of composition, while the solubility of danazol and mefenamic acid in the various oil–surfactant mixes was measured. It was noted that dilution of the emulsions led to apparent change in particle size distribution. The more hydrophilic oil–surfactant mixes showed a greater ease of emulsification and a lower particle size. It was also noted that multiple emulsions could be formed using systems of lower polarity. A linear relationship was observed between the hydrophile–lipophile balance (HLB) of the mix and the solubility of both danazol and mefenamic acid, with more hydrophilic mixes showing greater drug solubility values. The study has indicated that, within the range studied, more hydrophilic mixes tend to result in superior emulsification properties and greater drug solubility.

Introduction

Self-emulsifying drug delivery systems (SEDDS) may be defined as isotropic mixtures of oil, surfactant and drug that rapidly emulsify on mixing with water under conditions of gentle agitation. These systems have attracted considerable interest due to the possibility of improvement in bioavailability when drugs are administered in such formulations compared with conventional dosage forms (Lin et al 1991; Charman et al 1992; Shah et al 1994; Matusewka et al 1996; Sahm et al 1996; Porter & Charman 2001). However, there is currently no common consensus regarding the nature and proportionality of the oil–surfactant mix that is required to produce satisfactory emulsification, leading to a somewhat empirical approach to the formulation of SEDDS. Pouton (1985) has suggested that oils with intermediate polarity tend to exhibit better emulsification properties than comparatively lipophilic or hydrophilic materials, while Wakerly et al (1986) found that more hydrophobic surfactants based on glyceryl trioleate tended to produce smaller droplets on emulsification of Miglyol 812. The most significant attempt to systematically define the emulsification properties of oils has been that of Pouton (2000), whereby a classification scheme based on hydrophilicity in relation to emulsification properties was proposed. More specifically, surfactant-free lipid solutions are classified as Type I, with coarse dispersions formed on contact with an aqueous environment. For these systems the digestibility of the oil is considered to be more important than the emulsification properties of the oil. Type II systems contain relatively hydrophobic surfactants (hydrophilic–lipophilic balance (HLB) value < 12) and produce microemulsions in the 100–250-nm size range, while Type IIIA systems contain more hydrophilic surfactants (HLB > 12) and may contain co-solvents. Finally, Type IIIB systems contain a relatively low level of glyceride

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(<20%) and significant quantities of co-solvent (>50%), the surfactant involved being hydrophilic (HLB > 11). This classification system is undoubtedly a welcome advance in what is often a fairly empirical choice of system, although clearly it provides a starting point for rational formulation rather than a complete predictive tool. In particular, it is necessary to consider issues such as the behaviour of certain processed oils (particularly those that have been polyglycolysed) as these may have surfactant properties in their own right and hence may not act as typical Type I systems. The possibility of spontaneous multiple emulsion formation should also be considered. This has been previously noted for Labrafil systems (Craig et al 1996) and is potentially of interest due to the wide applicability of these emulsions. The generation of such droplets is merely noted in this study but the properties and formation mechanism of these systems is the subject of a separate communication.

A further issue concerns the ability of the SEDD systems to incorporate drugs. It is not yet clear whether it is necessary for the drug to be in solution within the oil–surfactant mixture or whether the absorption enhancement will also take place for suspended drugs. Abrams et al (1978) reported a discontinuation of the dose–absorption relationship of an emulsion formulation when the concentration of drug exceeded its solubility in the oil phase, while in contrast Barker et al (2003) reported a substantial increase in the absorption of α-tocopherol in Gelucire 44/14 in man despite the two components being phase separated. Either way there is a need for a greater knowledge of drug solubility in SEDD mixtures, as to date very few published studies have addressed this issue.

The objective of this study is to examine the use of a family of polyglycolysed glyceride-based oils, the Labrafils, that have been shown to be effective self-emulsifying systems (Craig et al 1995) but which also provide a reasonably well-controlled range of oils with which the influence of factors such as polarity and composition may be studied. The study will focus on two interrelated issues, namely the effect of composition on emulsification properties and the influence of choice of oil and surfactant on drug incorporation. In this manner it is intended that the ground rules regarding rational formulation for these systems may be further explored.

Materials and Methods

Materials

The properties and composition of the Labrafils (Gattefossé, France) used are listed in Table 1. In brief, the oils with lower-molecular-weight fatty-acid chains and a higher proportion of PEG showed greater hydrophilicity and hence higher HLB values. The oils were studied alone and in combination with Tween 80 (HLB 15) and Tween 20 (HLB 16.7) as specified (ICI, UK). Mefenamic acid powder was obtained from Sigma-Aldrich (Dorset, UK). This is a non-steroidal anti-inflammatory drug used for mild-to-moderate pain relief in the treatment of rheumatoid arthritis, osteoarthritis, dysmenorrhoea and menorrhagia. The aqueous solubility of the free acid is reported to be 40 μg mL^{-1} with log P = 5.3 and pK_a = 4.2 (TenHoor et al 1991). Danazol was used as obtained from Sigma-Aldrich (Dorset, UK) and is also a poorly water-soluble compound with an estimated aqueous solubility of <1 μg mL^{-1} and log P = 4.2 (Galia et al 1998). Danazol inhibits pituitary gonadotrophins and is used in the treatment of endometriosis, mammary dysplasia, gynaecomastia and other menstrual disorders.

Visual characterisation of the emulsification process

Oil–surfactant mixes were prepared (%v/v) ranging from 100% oil to 30% oil–70% surfactant. An oil–surfactant mix (250 μL) was added to 300 mL of distilled water in a 500-mL measuring cylinder with the pipette tip placed 1 cm above the meniscus of the water in the absence of applied mechanical agitation. The tendency to spread immediately after addition of the oil phase, the time required for oil incorporation within the bulk of the aqueous phase to occur and the appearance of the emulsions after single inversion of the cylinder were

Table 1 Physicochemical properties and main fatty acid composition of Labrafil oils (compiled from Gattefossé specification sheets).

Oil (MW)	Main fatty acid (%)	PEG group	HLB	Water solubility at 20 °C	Viscosity at 20 °C (m.Pa.s)
Labrasol (430)	Caprylic (C8) 50–80% Capric (C10) 20–50%	PEG 400	14	Soluble	80–110
Labrafac CM 10 (440)	Caprylic (C8) 50% Capric (C10) 50%	PEG 200	10	Dispersible	20–90
Labrafil WL 2609 BS (850)	Oleic (C18:1) 24–34% Linoleic (C18:2) 53–63%	PEG 400	6	Dispersible	80–120
Labrafil M 1944 CS (530)	Oleic (C18:1) 58–68% Linoleic (C18:2) 22–32%	PEG 8	4	Dispersible	75–95
Labrafil M 2125 CS (682)	Oleic (C18:1) 24–34% Linoleic (C18:2) 53–63%	PEG 6	4	Dispersible	70–90
Labrafac Lipophile WL 1349 (504)	Caprylic (C8) 50–80% Capric (C10) 20–50%	—	1	Insoluble	25–35

noted. Experiments were repeated four times at room temperature.

Microscopic examination of emulsion droplets

Emulsions were prepared by adding 250 μL of an oil–surfactant mix to 300 mL of distilled water and stirred for 10 min at 100 rev min^{-1} using a paddle method. Samples were drawn from the surface, middle and bottom of the beaker to obtain a fair representation of the structural variety of droplets (multiple droplets had a tendency to remain near the surface of the emulsion). A Differential Interference Contrast microscope, the Olympus BX 50, was employed with a Nikon-F-60 IM 35 mm camera.

Particle size analysis of emulsions droplets

An oil–surfactant mix (250 μL) ranging from 100% oil to 30% oil–70% surfactant (%v/v) was added to 300 mL of distilled water. Gentle mechanical agitation was applied using a rotor paddle set at 100 rev min^{-1} for 10 min. The Malvern Mastersizer S was used to measure particles in the micron size range. For each measurement, 2000–3000 sweeps were taken on an undiluted sample (unless otherwise stated). All samples prepared using the above protocol gave a suitable obscuration value, except for those emulsions indicated in the result tables. Four samples were prepared for each oil–surfactant composition and each was measured five times. The medium volume diameter and the span value (measures the width of the distribution) were recorded and averaged. Preliminary studies were conducted on emulsions prepared from 60% Labrafil M 1944 CS–40% Tween 80 diluted to 75%, 50% and 25% of the above concentration to establish whether dilution altered the measured size distribution; each diluted system had an obscuration value within the recommended 10–30% value recommended by the manufacturer. The Malvern Zetasizer was used in standard autosizer mode to measure emulsions with droplets in the submicron size range. Two measurements were taken on three separate samples of the same formulation (undiluted).

Solubilisation capacity determined by HPLC

The solubilities of the two drugs in all the oils under study and selected oil–surfactant mixes were measured. Fifty milligrams of drug was weighed into a 2-mL clear glass vial. Vehicle (1 mL) was added to each vial to which a suitable magnetic flea was added, with four repeats performed for each formulation. The vials were then placed in a Zinsser stem stirring–heating block for 24 h. The speed was set to 800 rev min^{-1} and the temperature adjusted to 25 °C. After 24 h, 250 μL of medium was removed from each vial and centrifuged at 20 000 rev min^{-1} for 15 min to separate the undissolved compound. Fifty microlitres of the clear medium was removed and diluted in 950 μL of the respective oil to achieve a 1:20 dilution. After a further 1:20 dilution into acetonitrile, 50 μL was added to the vial for HPLC analysis (Hewlett Packard series 1050). Mefenamic acid and danazol were analysed using a 25-cm Sperisorb ODS 25-μm column. The mobile phase for mefenamic acid comprised of 70% solvent A (90% acetonitrile–10% water–0.5% acetic acid) and 30% solvent B (10% acetonitrile–90% water–0.5% acetic acid) at a flow rate of 1 mL min^{-1}. Mefenamic acid was detected at 280 nm wavelength. The mobile phase for danazol was composed of 85% solvent A (90% acetonitrile–10% water) and 15% solvent B (10% acetonitrile–90% water) at a flow rate of 1 mL min^{-1}. Danazol was detected at 270 nm. A calibration curve was prepared for each drug over the range of 1000 μg mL^{-1} to 25 μg mL^{-1}, with a linear relationship observed. Samples containing oil and acetonitrile were analysed using the approach described above to determine whether the oil interferes with the detection wavelength for the drug. All experiments were repeated four times and then averaged. The solubility of the drug was also determined in distilled water and fasted simulated gastric and intestinal fluid (made up according to the method of Dressman et al (1998)).

Solubilisation capacity determined by visual analysis

To analyse the solubility of a compound by HPLC the drug has to remain in solution in the oil phase throughout the separation procedure. The eluting and dilution solvents must therefore be compatible with the oil–surfactant mix. For some oils and oil–surfactant mixes this was not possible with the current solvents employed. For these oils and oil–surfactant mixes an approximate determination of the solubility in a 1-mL mix was performed using visual analysis. The drug solubility for the following oils and oil–surfactant mixes were determined by visual observation: Labrafil M 1944 CS, Labrafil M 2125 CS, Labrafil WL 2609 BS, 50% Labrafil M 1944 CS–50% Tween 80 and 60% Labrafil M 2125 CS–40% Tween 80. To 1 mL of oil or oil–surfactant mix, drug was added in 1-mg increments from 3 mg to 25 mg. Each vial was stirred at 800 rev min^{-1} in a Zinsser stem stirring–heating block at 25 °C and assessed after 24 h. The experiment was repeated three times for each mix. The drug solubility in distilled water and simulated fasted gastric and intestinal fluid was also measured.

Statistical analysis

Statistical analysis of the effects of concentrations of surfactants (Tween 20 and Tween 80) on the particle size of the resultant emulsions was performed using Generalised Linear Modelling (SAS, Cary, NC). Three levels of surfactant were analysed: no surfactant, 20% and 60%. In all cases, post-hoc comparisons of the means of individual groups were performed, using Tukey's Honestly Significant Difference test. A significance level of $P < 0.05$ denoted significance in all cases. The analysis was performed using a response of particle size transformed by log10, due to the differences in scale of the measured particle sizes.

Results

Emulsification properties of Labrafils without surfactant

While particle size analysis has been routinely performed for SEDD systems, it was considered possible that the spontaneous formation of these systems may result in the size being dependent on both the method of preparation and dilution of the samples. The latter is particularly important as it is often necessary to dilute samples to achieve a suitable obscuration value. To this effect, preliminary studies were performed to establish whether further dilution could influence the measurements. As the emulsion was diluted, a reduction in the medium volume diameter value and an increase in the width of the distribution was noted (Table 2). Microscopic analysis showed a similar reduction in size of the droplets on dilution. To remove this variable, all samples were measured undiluted as indicated in the methodology section. This approach has the advantage of reliability in terms of sample preparation, although it carries the concomitant disadvantage of not being able to manipulate and optimise the obscuration via dilution. Furthermore, many of the emulsions had size ranges between the two instruments, again rendering reliable sizing difficult. This was an especially pertinent consideration, as some distributions were bimodal in nature, including size ranges for which neither the Mastersizer nor the PCS approach alone was appropriate. This, in turn, made it necessary for the operator to kill data channels to allow visualisation of one or other range. These systems are highlighted for the emulsions in question later in the text. A summary of visual observations, predominant emulsion structure and the average D (v, 0.5) (mean median diameter obtained from Mastersizer S) or the Z value (mean intensity diameter value based on the hydrodynamic radius of the particle, Malvern Zetasizer), as specified for the six Labrafil oils, are presented in Table 3.

Table 2 The effect of sample dilution on particle size of 60% Labrafil M 1944 CS–40% Tween 80 emulsions (obtained using the Malvern Mastersizer S).

60% Labrafil M 1944–40% Tween 80	Average D (v, 0.5) (μm)	Span
100% neat	43.9 (1.9)	2.56
75% dilution	36.1 (1.1)	2.66
50% dilution	26.2 (1.7)	3.35
25% dilution	17.9 (2.1)	3.98

Initial concentration, 250 μL in 300 mL distilled water. D (mean medium volume diameter obtained from the Malvern Mastersizer S by laser diffraction) presented as average with s.d. in parentheses.

There was a highly significant difference in particle size between oils ($P < 0.0001$), with the mean log particle size of the Labrafac Lipophile WL 1349, Labrafac CM 10 and Labrasol oils being significantly different from one another and all other oils ($P < 0.05$). The mean log particle size of the Labrafil M 1944CS, Labrafil WL 2609BS and Labrafil M 2125CS oils were not significantly different from one another, but were significantly different from the remaining 3 oils ($P < 0.05$). Of the six oils investigated, the most hydrophilic oil, Labrasol (HLB 14), showed the clearest tendency to self-emulsify, with excellent spreading properties and rapid cloud formation producing very small oil-in-water (o/w) droplets. Particle size analysis using the Malvern Zetasizer indicated droplet size values in the nanometer size range (average 145 nm). It should be noted that the apparent cloudiness of the system is not inconsistent with the Mastersizer data as the

Table 3 Characterisation of the emulsification of Labrafil oils in water including spreading propensity, incorporation time into the bulk aqueous phase, appearance on inversion, predominant droplet structure and particle size.

100% Oil	HLB	Spread on surface	Incorporation time (s)	Appearance on inversion	Emulsion character	Size (s.d.)	
						D (v, 0.5) (μm)	Z value (nm)
Labrasol	14	Yes	2	Very cloudy	Simple	—	145 (3.0)
Labrafac CM10	10	Yes	16	Cloudy	Multiple	13.8 (3.1)	—
Labrafil WP 2609 BS	6	No	180+	Cloudy	Simple[a]	42.9[b] (6.4)	—
Labrafil M 1944 CS	4	No	130	Cloudy	Multiple	43.9[b] (1.9)	—
Labrafil M 2125 CS	4	No	120	Cloudy	Multiple	49.7[b] (3.9)	—
Labrafac Lipophile WL 1349	1	No	[c]	Clear	Multiple	268.5 (26)	—

[a]Formulations contained predominantly o/w droplets but a few w/o/w droplets were also observed. [b]Bimodal distributions were observed for these emulsions representing smaller o/w and larger w/o/w multiple droplets. Data channels representing the smaller droplets were killed/removed from the calculation to obtain the medium diameter of the larger peak. [c]Oil–surfactant mix turned cloudy but remained at the surface, no visual cloudy streaks were observed thus no time was recorded. D (v, 0.5) (μm) is the mean medium volume diameter obtained from the Malvern Mastersizer S by laser diffraction. Z value (nm) is the mean intensity diameter obtained from the Malvern Zetasizer by photon correlation spectroscopy.

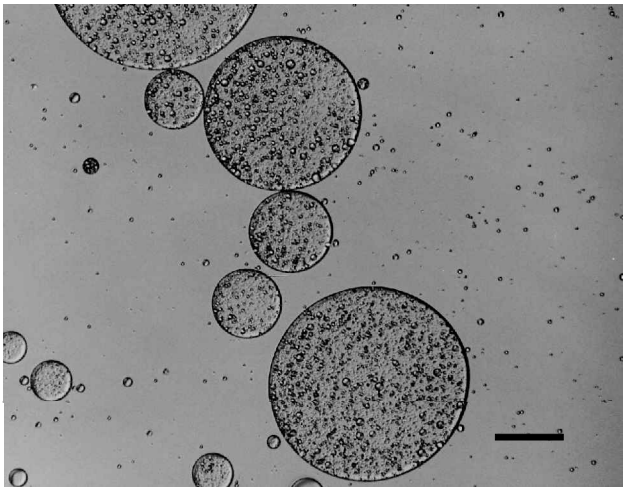

Figure 1 Example of a multiple emulsion droplet formed from Labrafil M1944 CS. Bar represents 100 μm.

presence of a small number of large particles can result in visible cloudiness. Labrafac CM10 (HLB 10), another polar oil, displayed excellent spreading properties, although multiple droplets were produced with mean D (v, 0.5) of 13.8 μm. Labrafil WL 2609 BS, of intermediate polarity (HLB 6), displayed poor self-emulsifying properties, while hydrophobic oils such as Labrafil M 1944 CS (HLB 4) and Labrafil M 2125 CS (HLB 4) displayed poor spreading characteristics and took longer for incorporation compared with Labrasol and Labrafac CM 10, but a shorter time than Labrafil WL 2609 BS. For both Labrafil WL 1944 CS and Labrafil M 2125 CS, the predominant droplet structure was multiple in nature (an example is given in Figure 1), although simple o/w droplets were also noted under the microscope. The most hydrophobic oil, Labrafac Lipophile WL 1349 (HLB 1), did not self-emulsify well and produced large multiple droplets. After formation these droplets migrated to the air–water interface, thereby leaving a clear bulk phase.

Emulsification of oil–surfactant mixes

A summary of visual observations, emulsion type and particle size for all six Labrafil oils in combination with Tween 80 are presented in Table 4. The statistical significance of the differences in particle size varied according to the composition, with highly significant ($P < 0.0001$) differences between oils seen for the majority of surfactant contents. Figure 2 shows the relationship between the log particle size and the HLB of the mixes for both the Tween 80 and Tween 20 systems. Interestingly, there appears to be two populations whereby higher HLB mixes (>ca 8) show a markedly smaller size than emulsions produced from more hydrophobic mixes. The data also indicates that the more hydrophilic oils produced emulsions that became incorporated into the aqueous phase rapidly, although this trend was apparently contradicted for the Labrafac Lipophile WL 1349. However, this oil was not easily miscible with Tween 80 and the binary liquid produced streaks within the bulk aqueous phase on addition, hence the fast incorporation times are not a reflection of emulsification as such.

Multiple emulsion droplets were observed for all oil–surfactant combinations between 100% oil and 30% oil–70% surfactant for Labrafac Lipophile WL 1349, Labrafil M 2125 CS and Labrafil M 1944 CS. For these oils, it was evident that the number and size of multiple droplets decreased as the surfactant ratio, and hence overall hydrophilicity of the system, was increased. The presence of multiple droplets, though few in number, were also detected for Labrafil WL 2609 BS for oil–surfactant ratios 100% oil to 50% oil–50% surfactant. Thereafter, multiple droplets were not detected. These results indicate the possibility of multiple emulsion formation over a wide oil–surfactant range for oils of different structural composition. As mentioned previously, multiple droplets were also noted for 100% Labrafac CM 10 emulsions, although the effect was lost on addition of Tween 80. In contrast, multiple droplets were absent for all Labrasol formulations, which produced only simple o/w droplets. These results suggest the formation of multiple droplets is dependent on the oil employed and the oil–surfactant ratio, with the more hydrophobic systems and lower surfactant ratios tending to result in the formation of such systems.

Emulsions were then prepared from the same range of oils using the more hydrophilic surfactant Tween 20, with the results summarised in Table 5. The trends were similar to those seen for the Tween 80 systems, in that the more hydrophilic oils exhibited smaller particle sizes and a greater tendency to form simple, rather than multiple, emulsions. Similarly, the inclusion of a greater proportion of surfactant resulted in clearer emulsions and lower sizes.

Solubility studies

The results of the solubility studies are shown in Table 6. The data indicate that the solubility is related to the hydrophilicity of the oil or oil–surfactant mixture, with more hydrophilic systems resulting in greater solubility values. To investigate this relationship further, the HLB value of the oil–surfactant mixes was calculated from simple proportional addition and the results displayed in Figure 3. A linear relationship was observed between the polarity of the oil or oil–surfactant mix expressed in terms of the hydrophile–lipophile balance and the solubility.

Discussion

The study has indicated three main points that may be of relevance to the formulation of SEDDS. In the first instance, the emulsification properties appear to be highly dependent on composition, with higher HLB oil and surfactant systems in combination with high surfactant content resulting in smaller droplets. The composition dependence of SEDD emulsification has already been

Table 4 Characterisation of the emulsification of Labrafil oils with Tween 80 in water including incorporation time into the bulk aqueous phase, appearance on inversion and predominant droplet structure and particle size.

Oils	% Tween 80						
	10	20	30	40	50	60	70
Labrasol (HLB 14)							
Incorp. time (s) and appearance	22 S Cloudy	23 Cloudy	22 Clear	23 Clear	34 Clear	31 Clear	44 Clear
Predom. emul. type	S	S	S	S	S	S	S
Particle size (s.d.)	Z 79 (7) nm	Z 51 (10) nm	[a]	[a]	[a]	[a]	[a]
Labrafac CM10 (HLB 10)							
Incorp. time (s) and appearance	2 V Cloudy	23 S Cloudy	21 VS Cloudy	23 VS Cloudy	22 VS Cloudy	Immediate VS Cloudy	Immediate Clear
Predom. emul. type	S	S	S	S	S	S	S
Particle size (s.d.)	Z 254 (5) nm	Z 192 (6) nm	Z 154 (6) nm	Z 91 (4) nm	[a]	[a]	[a]
Labrafil SL 2609 BS (HLB 6)							
Incorp. time (s) and appearance	180+ V Cloudy	123 Cloudy	115 Cloudy	50 Cloudy	66 S Cloudy	82 S Cloudy	96 VS Cloudy
Predom. emul. type	S[b]	S[b]	S[b]	S[b]	S[b]	S	S
Particle size (s.d.)	[c]	[c]	Z 572 (50) nm	Z 682 (31) nm	Z 713 (54) nm	Z 570 (29) nm	Z 429 (24) nm
Labrafil M 1944 CS (HLB 4)							
Incorp. time (s) and appearance	74 V Cloudy	61 V Cloudy	21 Cloudy	25 V Cloudy	17 Cloudy	22 S Cloudy	21 S Cloudy
Predom. emul. type	M	M	M	M/S	S	S	S
Particle size (s.d.)	D 47 (2) μm	D 48 (2) μm	D 44 (8) μm	D 36 (1) μm Z 444 (31) nm	Z 438 (27) nm	Z 365 (40) nm	[a]
Labrafil M 2125 CS (HLB 4)							
Incorp. time (s) and appearance	86 Cloudy	21 Cloudy	19 V Cloudy	17 V Cloudy	16 V Cloudy	17 Cloudy	29 S Cloudy
Predom. emul. type	M	M	M	M/S	S	S	S
Particle size (s.d.)	D 57 (4) μm	D 70 (12) μm	D 45 (9) μm Z 560 (60) nm	D 30 (4) μm Z 432 (15) nm	Z 425 (30) nm	Z 427 (17) nm	Z 372 (19) nm
Labrafac Lipophile WL 1349 (HLB 1)							
Incorp. time (s) and appearance	8 S Cloudy	6 S Cloudy	4 Cloudy	27 V Cloudy	32 Cloudy	22 S Cloudy	25 VS Cloudy
Predom. emul. type	M	M	M	S	S	S	S
Particle size (s.d.)	D 177 (4) μm	D 143 (8) μm	D 10 (18) μm	Z 240 (2) nm	Z 212 (9) nm	Z 116 (6) nm	Z 65 (6) nm

[a] Merit value below detection of instrument. [b] A few multiple droplets also observed. [c] The micron peak was a split peak so the D (v, 0.5) value could not be measured. Emulsion type: S = simple; M = multiple droplets. Particle size: s.d. = standard deviation. Appearance: S Cloudy = slightly cloudy; V Cloudy = very cloudy; VS Cloudy = very slightly cloudy. D (v, 0.5) (μm) is the mean medium volume diameter obtained from the Malvern Mastersizer S by laser diffraction. Z value (nm) is the mean intensity diameter obtained from the Malvern Zetasizer by photon correlation spectroscopy.

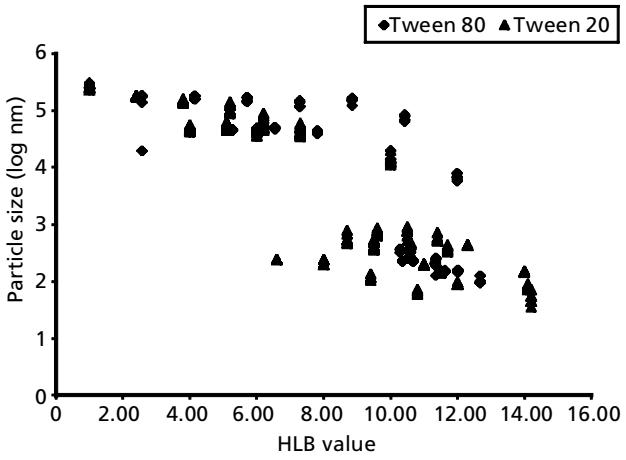

Figure 2 Relationship between log particle size (nm) of emulsion droplets and HLB of the mix for systems containing Tween 80 and Tween 20.

noted (Groves & DeGalindez 1976; Pouton 1985; Wakerly et al 1986), although the earlier studies have indicated that more hydrophobic systems tend to produce finer emulsions. In the present case, the HLB of the oil showing the best properties is relatively high (Labrasol, HLB 14). However, the oils under study here do have some intrinsic surfactant properties due to the glycolysation, hence over and above HLB the distribution and miscibility of polar groups may be of importance. In parallel to this, the study has indicated that more hydrophobic oil systems tend to result in the formation of multiple emulsions. While the formation of these structures will form the basis of a separate communication, both their appearance and the HLB dependence of their generation are noteworthy.

The second highlighted issue concerns the difficulties associated with particle sizing of SEDDS. In particular, there is some cause for concern in that dilution of the emulsions may result in changes in particle size, hence reliable assessment of diameter is a non-trivial issue. In this study, we have taken the approach of standardising the preparation method to achieve some degree of parity between data sets. The difficulties associated with this approach are apparent. In particular it was found that in some cases the obscuration is inappropriate for the measurement on one or other instrument. Nevertheless, the study has indicated that caution is required when measuring the particle size of self-emulsifying systems, with dilution to fit the obscuration range of instrument carrying the concomitant and perhaps unreliable assumption of the size being independent of concentration.

Finally, the solubility studies have resulted in the unexpected observation of linearity between the drug solubility and the HLB of the oil–surfactant mix. This is of interest in terms of the practicalities of formulation as it may be essential to maximise the drug solubility in the mixture before emulsification. In this context, the observation is interesting in that it may be reasonable to assume that the surfactant may have the effect of enhancing the solubility of the drug in the droplet, possibly due to reverse micelle formation. The data presented here indicate that, in fact, any enhancement is due to changes in the HLB rather than any specific colloidal properties of the surfactant. The majority of studies within the pharmaceutical literature have studied the solubility of drugs in aqueous systems due to the obvious relevance to formulation and biodistribution, with fewer studies being concerned with non-aqueous systems. The solubility of drugs in aqueous micellar solutions may be given by either the two-state or mass-action models and the extent of incorporation described by the solubilization ratio (SR), according to equation 1.

$$SR = ([D]_t - C_s)/([BS]_t - CMC) \quad (1)$$

where C_s is the solubility of the drug, $[D]_t$ is the total concentration in solution, $[BS]_t$ is the bile salt concentration and CMC is the critical micelle concentration (Wiedman & Kamel 2002). This approach, therefore, does not anticipate the linearity of the relationship seen here between the HLB of the mixes and solubility, particularly given the chemical diversity of the systems in question. In fact the behaviour is more akin to a non-aqueous co-solvent system in that the polarity appears to be the determining factor dictating the solubility. This in turn suggests that the behaviour may be described by regular solution theory that classically predicts that the solubility of a solute (1) in a solvent (2) is given by:

$$-\log X_2 = \frac{\Delta H_F}{2.303R}\frac{T_0 - T}{T} - \frac{V_2\phi_1^2}{2.303RT}(\delta_1 - \delta_2)^2 \quad (2)$$

where X_2 is the molar solubility, ΔH_F is the heat of fusion of the solute, R is the gas constant, T_0 is the melting point of the solute and T is the experimental temperature, ϕ_1 is the volume fraction of solvent and δ is the solubility parameter of the solvent/solute (Hildebrand & Scott 1950). This parameter is the square root of the cohesive energy density and may be used to predict solubility in that, in theory, the more similar the values for the two components, the higher the solubility. There is a considerable body of literature available whereby solubility parameters have been investigated as a means of predicting drug solubility (e.g. Stengele et al 2001), particularly in the context of transdermal delivery (e.g. Du Plessis et al 2002). Perhaps surprisingly the approach has not been extensively used as a means of predicting drug solubility in emulsions or self-emulsifying systems, possibly because the presence of the surfactant is considered to render such an approach inappropriate. Our data suggest that in fact such an approach may be of considerable use, given the clear relationship between polarity and drug incorporation using the two model systems under study here.

Conclusions

The study has shown that the emulsification properties of Labrafil/Tween based self emulsifying systems are highly dependent on composition, with more hydrophilic mixtures showing a greater tendency to form emulsions of

Table 5 Characterisation of the emulsification of Labrafil oils with Tween 20 in water, including incorporation time into the bulk aqueous phase, appearance on inversion, predominant droplet structure and particle size.

Oil	% Tween 20						
	10	20	30	40	50	60	70
Labrafac CM10 (HLB10)							
Incorp. time (s) and appearance	2 V Cloudy	2 V Cloudy	3 Cloudy	9 S Cloudy	12 Clear	17 Clear	17 Clear
Predom. emul. type	S	S	S	S	S	S	S
Particle size (s.d.)	Z 226 (5) nm	Z 209 (9) nm	Z 150 (4) nm	Z 103 (15) nm	[a]	[a]	[a]
Labrafil WL 2609 BS (HLB 6)							
Incorp. time (s) and appearance	180+ V Cloudy	123 Cloudy	125 Cloudy	46 Cloudy	52 S Cloudy	34 S Cloudy	21 VS Cloudy
Predom. emul. type	S[b]	S[b]	S[b]	S[b]	S	S	S
Particle size (s.d.)	[c]	[c]	[c]	Z 356 (31) nm	Z 204 (54) nm	[a]	[a]
Labrafil M 1944 CS (HLB 4)							
Incorp. time (s) and appearance	59 Cloudy	21 V Cloudy	16 V Cloudy	9 V Cloudy	12 Cloudy	23 Cloudy	25 S Cloudy
Predom. emul. type	M	M	M	M/S	S	S	S
Particle size (s.d.)	D 45 (1) μm	D 48 (2) μm	D 42 (2) μm	D 43 (3) μm Z 339 (15) nm	Z 226 (2) nm	Z 149 (4) nm	[a]
Labrafac Lipophile WL 1349 (HLB 1)							
Incorp. time (s) and appearance	27 S Cloudy	18 S Cloudy	11 S Cloudy	9 Cloudy	8 Cloudy	11 Cloudy	14 Cloudy
Predom. emul. type	M	M	M	M	M	M	S
Particle size (s.d.)	D 173 (24) μm	D 169 (13) μm	D 157 (15) μm	D 131 (16) μm	D 148 (18) μm	D 74 (10) μm	D 7 (1) μm

[a]Merit value below detection of instrument. [b]A few multiple droplets also observed. [c]The micron peak was a split peak so the D (v, 0.5) value could not be measured. Emulsion type: S = simple; M = multiple droplets. Particle size: s.d. = standard deviation. Appearance: S Cloudy = slightly cloudy; V Cloudy = very cloudy; VS Cloudy = very slightly cloudy. D(v, 0.5) (μm) is the mean medium volume diameter obtained from the Malvern Mastersizer S by laser diffraction. Z value (nm) is the mean intensity diameter obtained from the Malvern Zetasizer by photon correlation spectroscopy.

Table 6 Solubility of mefenamic acid and danazol in Labrafil–Tween systems.

Formulation (HLB)	HLB	Mefenamic acid average solubility ($mg\,mL^{-1}$) (s.d.)	Mefenamic acid molar solubility ($mol\,L^{-1}$)	Danazol average solubility ($mg\,mL^{-1}$) (s.d.)	Danazol molar solubility ($mol\,L^{-1}$)
100% Labrasol	14	20.3 (2.3)	0.084	39.1 (2.7)	0.117
100% Labrafac CM 10	10	14.9 (1.8)	0.062	24.9 (0.3)	0.074
100% Labrafil WL 2609 BS	6	9.0 (1.0)	0.037	14.0 (1.0)	0.041
100% Labrafil M 1944 CS	4	5.0 (1.0)	0.021	8.0 (1.0)	0.024
100% Labrafil M 2125 CS	4	5.0 (1.0)	0.021	8.0 (1.0)	0.024
100% Labrafac Lipophile WL 1349	1	2.4 (0.03)	0.010	6.4 (0.06)	0.019
90% Labrasol–10% Tween 80	14.1	22.9 (0.9)	0.095	34.8 (0.6)	0.103
90% Labrafac CM 10–10% Tween 80	10.5	18.9 (1.3)	0.078	25.5 (0.5)	0.076
50% Labrafil M 1944 CS–50% Tween 80	9.5	17.0 (1.0)	0.070	19.0 (1.0)	0.056
60% Labrafil M 2125 CS–40% Tween 80	8.4	15.0 (1.0)	0.062	17.0 (1.0)	0.050
60% Labrafac Lip 1349–40% Tween 80	6.6	10.1 (0.08)	0.042	15.3 (0.6)	0.045
Distilled water	—	0.033 (<0.01)	$<10^{-5}$	0.007 (<0.01)	$<10^{-5}$
Fasted simulated gastric fluid	—	0.003 (<0.01)	$<10^{-5}$	0.078 (<0.01)	$<10^{-5}$
Fasted simulated intestinal fluid	—	0.046 (<0.01)	$<10^{-5}$	0.008 (<0.01)	$<10^{-5}$

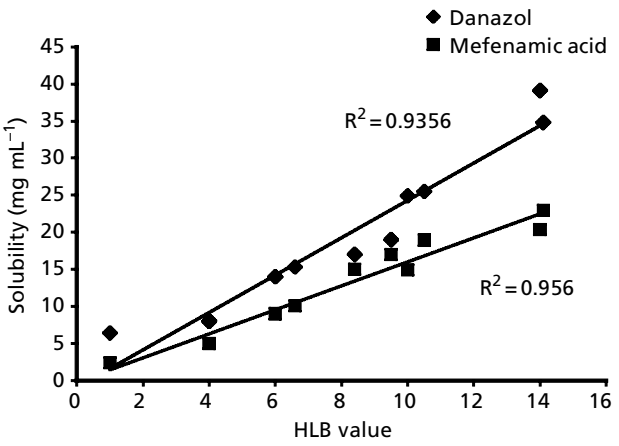

Figure 3 Relationship between the solubility of mefenamic acid and danazol in Labrafils and Labrafil/surfactant mixes and HLB value of the solvent.

small particle size. In addition, such mixtures allow greater solubilisation of two model hydrophobic drugs. The investigation has also highlighted the difficulties associated with the measurement of particle size for SEDD systems, as dilution of the emulsion may result in changes in particle size.

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