International Journal of Pharmaceutics, 27 (1985) 311–323
Elsevier

IJP 00923

Phase transitions in ternary systems and oil-in-water emulsions containing cetrimide and fatty alcohols

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(Received June 6th, 1985)
(Modified version received August 6th, 1985)
(Accepted August 8th, 1985)

Key words: cream stability – emulsion stability – fatty alcohols – differential scanning calorimetry – rheology – polymorphism – ternary surfactant/fatty alcohol/water phases – gel phases

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Summary

Differential scanning calorimetry (D.S.C.) was used to investigate phase transitions in stable and unstable emulsions prepared with cetrimide/fatty alcohols. Ternary systems, formed by interacting cetrimide and fatty alcohol in water and chosen to represent the continuous phases of the corresponding emulsions, were also investigated. Stability was followed using rheological techniques. The ternary systems prepared from each alcohol showed similar properties to the corresponding emulsions. All systems were semisolid immediately after preparation. Thus flow curves were in the form of anticlockwise hysteresis loops and apparent viscosities high. On storage, the cetostearyl alcohol systems remained semisolid and stable, whereas the pure alcohol systems became mobile and emulsions eventually separated. In unstable systems, flow curves changed and apparent viscosities reduced. The D.S.C. data for each ternary system gave similar transitions to those of the corresponding emulsion. In the stable cetostearyl alcohol ternary system and emulsion, two broad endotherms were present. These did not alter over the 30-day testing period. In contrast, the unstable pure alcohol ternary systems and emulsions, showed several endothermic transitions, which changed as systems aged and became mobile. The D.S.C. results correlated well with microscopic and rheological experiments from previous work. They imply that emulsion continuous phases, formed from the interaction of cetrimide and fatty alcohol in water can exist in several forms, each

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stable over definite temperature ranges depending on alcohol chain length and homologue composition. A stable emulsion will form only when one of these, the viscoelastic gel phase, is stable at storage temperature.

Introduction

In the formulation of oil-in-water emulsions of pharmaceutical and cosmetic interest, wide use is made of mixed emulsifiers of the surfactant/fatty alcohol type. The surfactant and alcohol may be incorporated already blended as an emulsifying wax, or may be added separately during the heating and cooling cycle of manufacture. Stable emulsions may be prepared of any desired consistency, from mobile lotions to stiff creams by increasing the mixed emulsifier concentration.

For economic reasons, cetostearyl alcohol or commercial mixtures of cetyl or stearyl alcohols are often used. Their modes of action are assumed to be similar so that many formulations do not distinguish between pure cetyl or stearyl alcohols and commercial grades, even though the latter may contain up to 30% of other homologues (Mace, 1975). However, experimental data do not support this assumption. Oil-in-water creams prepared with ionic or non-ionic surfactants and pure cetyl or stearyl alcohols are considerably less stable than those prepared with homologue admixtures such as cetostearyl alcohol (Barry, 1970; Eccleston, 1976, 1977a and b, 1982, 1984). Pure alcohols do not form stable, semisolid creams. This is relevant when it is considered that fatty materials from petroleum based sources are often very pure from the homologue point of view. Batches of established cream and lotion formulations may fail unexpectedly due to the greater homologue purity of the alcohol used. Production difficulties are compounded with some surfactant/fatty alcohol combinations as the instability is not readily apparent immediately after preparation, but develops with time (Eccleston, 1976).

The present work extends previous rheological and microscopical studies and includes differential scanning calorimetry (D.S.C.) to investigate phase transitions in unstable and stable cetrimide emulsions formulated with pure and mixed homologue alcohols. Cetrimide was used for this study, as it is the surfactant chosen for many semisolid preparations, and marked instabilities occur when it is combined with pure fatty alcohols (Eccleston, 1976, 1977a).

Ternary systems, formed by dispersing the mixed emulsifier in water, without the addition of an oil phase, and prepared to represent the continuous phase of the corresponding emulsion, were also examined. Pure alcohol ternary systems were not investigated previously.

Materials and Methods

Materials

Cetrimide B.P. was obtained from I.C.I. (U.K.). Liquid paraffin and the alcohols hexadecanol (C_{16}, cetyl) octadecanol (C_{18}, stearyl) and cetostearyl alcohol B.P. were as described previously (Eccleston, 1982). G.L.C. analysis showed that the nominal purities of the cetyl and stearyl alcohols were better than 99%, and that cetostearyl alcohol contained mainly stearyl (54%) and cetyl (33%) alcohols with some tetradecanol (C_{14}, 8.4%) and a trace of dodecanol (~ 1.5%).

Preparation of ternary systems and emulsions

A ternary system (cetrimide 2.8 g; fatty alcohol 25.2 g; water 300 g) and emulsion (liquid paraffin 100 g; cetrimide 2.8 g; fatty alcohol 25.2 g; water 300 g) was prepared from each alcohol by mixing the hot excipients at 70°C, and then cooling whilst still mixing to the storage and testing temperature of 25°C (Barry and Saunders, 1970a). The concentration of mixed emulsifier (~ 6.5%) was chosen because with cetostearyl alcohol it produces a 'soft' semisolid cream of a similar consistency to that used in many commercial preparations.

Continuous shear experiments

Ternary systems and emulsions were examined at 25°C using a Ferranti Shirley cone-and-plate viscometer in conjunction with an automatic flow recorder unit designed to produce a standardized shear procedure, and an X-Y plotter. All systems were examined immediately after preparation, and throughout the next 30 days using a maximum shear rate of 1684 s^{-1} and a sweep time of 600 s.

Differential scanning calorimetry

D.S.C. experiments between 0 and 100°C were performed throughout the 30-day testing period using the DuPont 910 D.S.C. system with the 990 programmer/recorder. The samples and reference (water) were placed in hermetically sealed pans. It was difficult to adjust the weight of water in the reference pan with the precision needed to eliminate the initial base line drift completely. Thus cooling runs were also made on fresh samples (from approximately 35–0°C) to check for additional transitions that would be masked by the initial baseline drift during a normal heating run.

Preliminary experiments were also performed to find the optimum combination of sample size and scan speed for comparing the systems. It was found that a scan speed of 10°/min and 10 mg sample size gave the best compromise between resolution, temperature accuracy and attenuation.

Results

The ternary systems prepared from each alcohol showed similar properties to the corresponding emulsions. All systems were mobile semisolids when first prepared. However, whereas the cetostearyl alcohol emulsion and ternary system remained stable and semisolid on storage, the pure cetyl or stearyl alcohol systems eventually broke down to form mobile liquids. This breakdown was most marked with stearyl alcohol, where the cream showed signs of separation after two weeks. These changes,

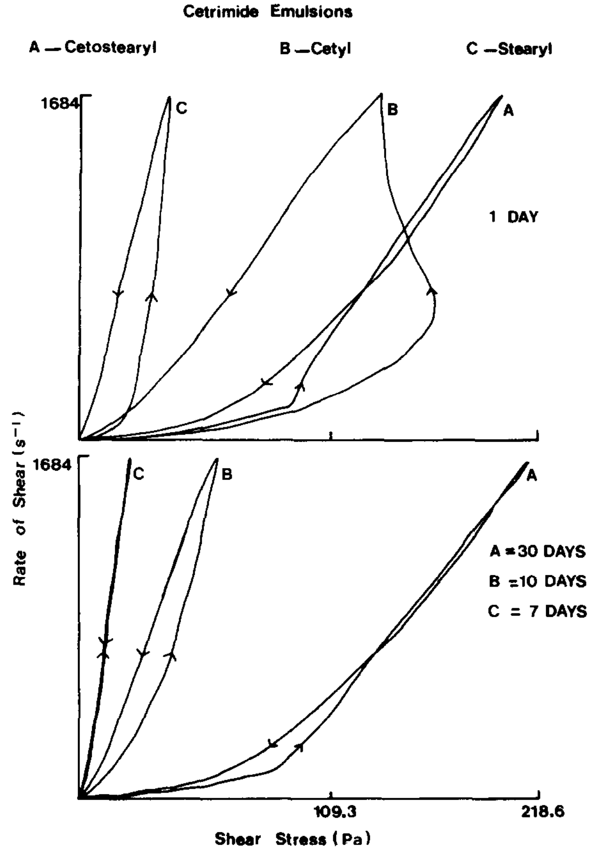

Fig. 1. Ferranti-Shirley cone and plate viscometer. Flow curves for cetrimide emulsions: (top) after 24 h and (bottom) aged for the stated times.

and the timescale over which they occurred are illustrated by the rheological data (in Figs. 1 and 2, and Table 1).

Initially each emulsion was semisolid so that the flow curves are in the form of anticlockwise hysteresis loops, or are complex, as for cetostearyl alcohol (Fig. 1). Although such flow curves provide useful information, their interpretation should be treated with caution. This is because they are not a measure of any fundamental property of the system, but rather the complex phenomenon of structure breakdown. The position of the curves and apparent viscosities η_{app} derived from the apex of the loops (Table 1) do, however, confirm that after only 24 h the cetostearyl alcohol cream is more resistant to structure breakdown than the cetyl alcohol cream which in turn is more resistant than the stearyl alcohol cream.

After one month storage at 25°C, the consistency of the cetostearyl alcohol cream had not changed significantly, thus the 30-day flow curves and η_{app} values are similar to those obtained after 24 h. In contrast, as the pure alcohol emulsions broke down to form mobile liquids, they showed less resistance during the standardized

TABLE 1

VARIATION OF APPARENT VISCOSITY AT THE LOOP APEX, η_{app} ($\times 10^{-1}$ Pa·s) WITH STORAGE TIME FOR TERNARY SYSTEMS (TS) AND EMULSIONS (E)

Storage (days)	Cetostearyl alcohol		Cetyl alcohol		Stearyl alcohol	
	TS	E	TS	E	TS	E
0	0.857	1.08	–	0.908	0.130	0.325
1	0.960	1.25	0.870	0.750	0.130	0.260
2	–	1.22	0.727	0.739	0.130	0.233
3	0.922	–	0.597	0.584	0.130	0.156
7	0.987	1.27	0.409	0.467	*	*
10	0.987	–	0.389	0.402		
14	0.987	1.27	*	*		
21	0.987	–				
30	0.987	1.27				

* Very mobile or separated.

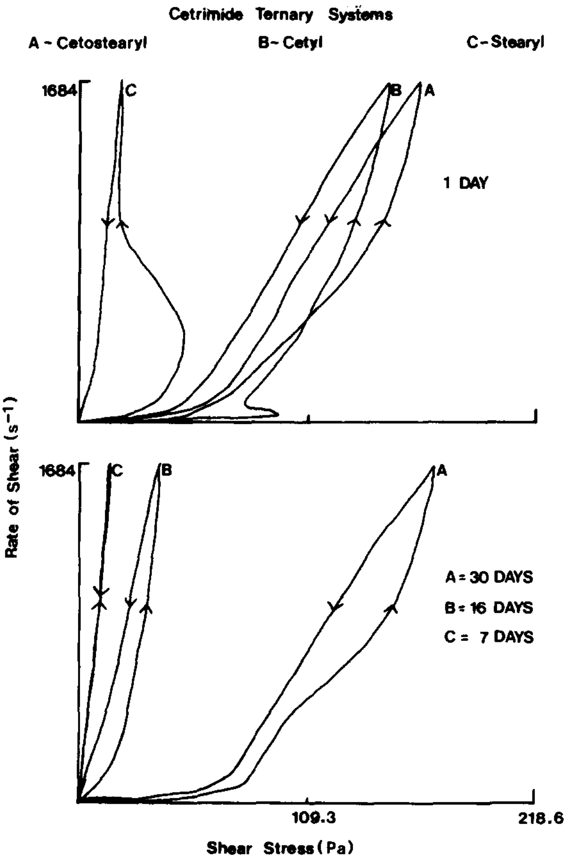

Fig. 2. Ferranti-Shirley cone and plate viscometer. Flow curves for cetrimide ternary systems: (top) after 24 hours and (bottom) aged for stated times.

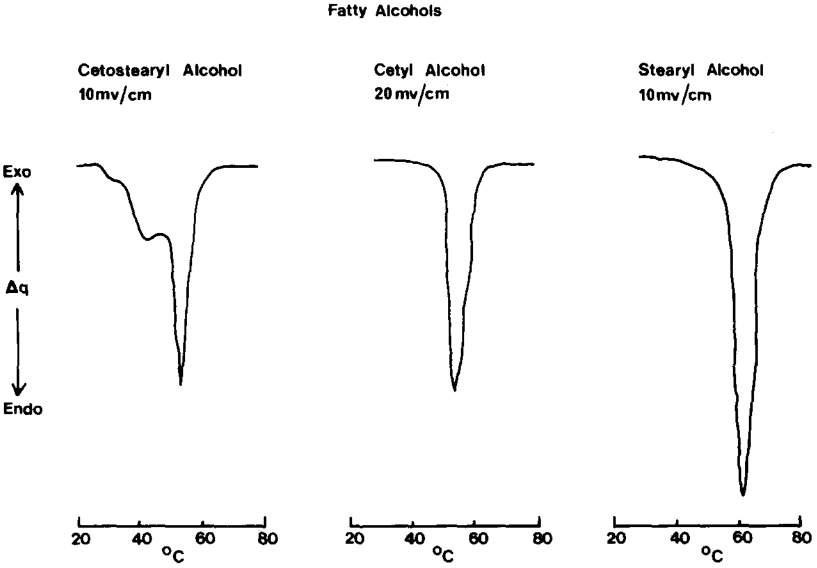

Fig. 3. D.S.C. data for fatty alcohols.

shearing cycle, the curves moved to lower shear stress values, and loop areas and η_{app} reduced. This occurred during approximately 10 days for the cetyl and 7 days for the stearyl alcohol emulsions. Thereafter the emulsions became so mobile that tests were not continued.

The flow curves and η_{app} for the corresponding ternary systems shown in Fig. 2 and Table 1 confirm that the ternary systems break down in a similar manner to the emulsions. Initially, as with the emulsions, they were all semisolid so that flow curves are in the form of hysteresis loops and η_{app} values relatively high. On ageing, the cetostearyl alcohol ternary system did not change so that the initial and 30-day flow curves are similar. In contrast, the pure alcohol ternary systems broke down to thin liquids in a similar manner to the corresponding emulsions, so that η_{app} values and loop areas reduced (cf. Fig. 1).

D.S.C. experiments were performed over the time scale at which the ternary systems and emulsions thinned and broke down. Data for the fatty alcohols alone are shown in Fig. 3. The pure alcohols show a single endotherm, peaking at 56°C for cetyl and 63°C for stearyl alcohol. With cetostearyl alcohol, there is an endotherm peaking at 55°C with a broad asymmetric shoulder at the temperature range 30–45°C.

Fig. 4 shows the data for the stable semisolid cetostearyl alcohol ternary system and emulsion after 1 and 30 days' storage at 25°C. The systems showed relatively simple thermal spectra which did not change after 30 days. In each system, there is a major endotherm (starting around 45–50°C and peaking at 63°C) and usually a broad asymmetric low temperature transition, in the range ~ 14–45°C.

In contrast, the unstable pure alcohol systems produced several endothermic transitions, as systems thinned and broke down. Fig. 5 shows data for the pure cetyl

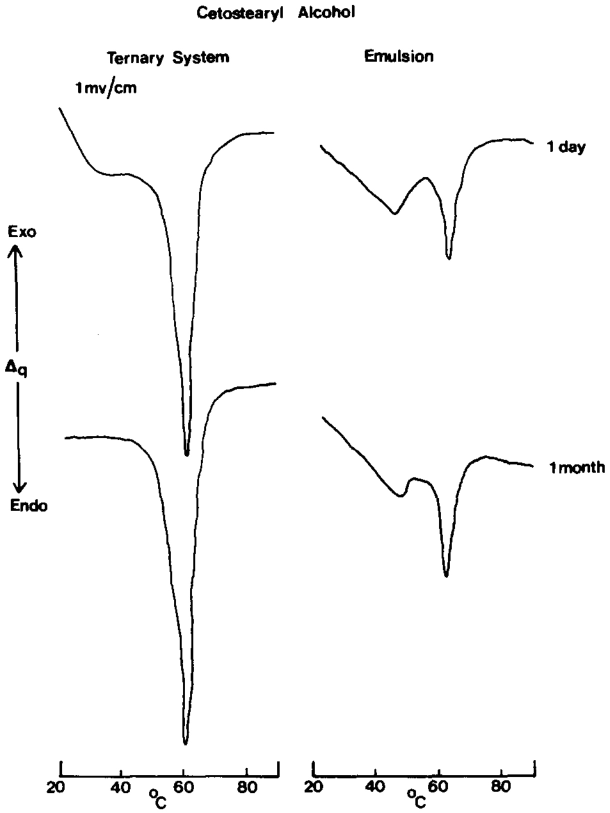

Fig. 4. Cetostearyl alcohol ternary system and emulsion. D.S.C. data after storage at 25°C for stated times.

alcohol system. Initially, the ternary system is semisolid, and the spectrum obtained is essentially similar to that obtained for the cetostearyl alcohol ternary system (cf. Fig. 4), i.e. there is a broad high temperature transition peaking as a doublet close to 60°C and a weak, broad, low temperature endotherm. As the ternary system breaks down and becomes mobile, the high temperature transition diminishes somewhat and the low temperature endotherm at 38°C develops and increases in intensity so that it is prominent in the mobile ternary system.

Data for the cetyl alcohol emulsion over the first 10 days, when it changed from a semisolid to a thin, milky fluid, are also shown in Fig. 5. Initially, as with the cetostearyl alcohol emulsion (Fig. 4) there is a high temperature endotherm, resolved here as a doublet at ~ 60°C, with a broad shoulder peaking at 39°C. As the cream breaks down, the low temperature endotherm at 39°C develops and increases in intensity. Concurrently, the high temperature endotherm reduces so that after 10 days it has almost disappeared.

The unstable pure stearyl alcohol ternary system and emulsion showed similar trends as they aged to the cetyl alcohol system (Fig. 6). As the stearyl alcohol ternary

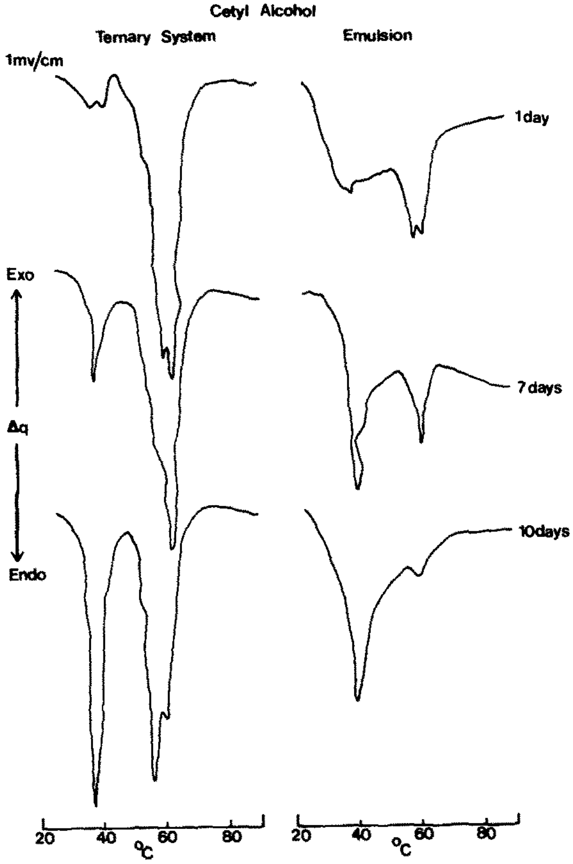

Fig. 5. Pure cetyl alcohol ternary system and emulsion. D.S.C. data after storage at 25°C for stated times.

system thinned, a low temperature endotherm developed at 45°C and resolved as a doublet as it increased in intensity, and the high temperature endotherm at 66°C reduced somewhat. With the stearyl alcohol emulsion, the broad low temperature endotherm was prominent even 3 h after preparation, and the high temperature endotherm is reduced. This correlates with the rheological data which implies that even in fresh semisolid stearyl alcohol systems, the structure is less resistant to breakdown than the other alcohol systems. The high temperature endotherm had disappeared after 7 days.

Discussion

The similarities between the rheological and D.S.C. data for each ternary system and its corresponding emulsion throughout the testing period support the theory that each ternary system is structurally similar to the continuous phase of the corresponding emulsion.

Ternary systems were prepared by mixing molten alcohol with aqueous cetrimide

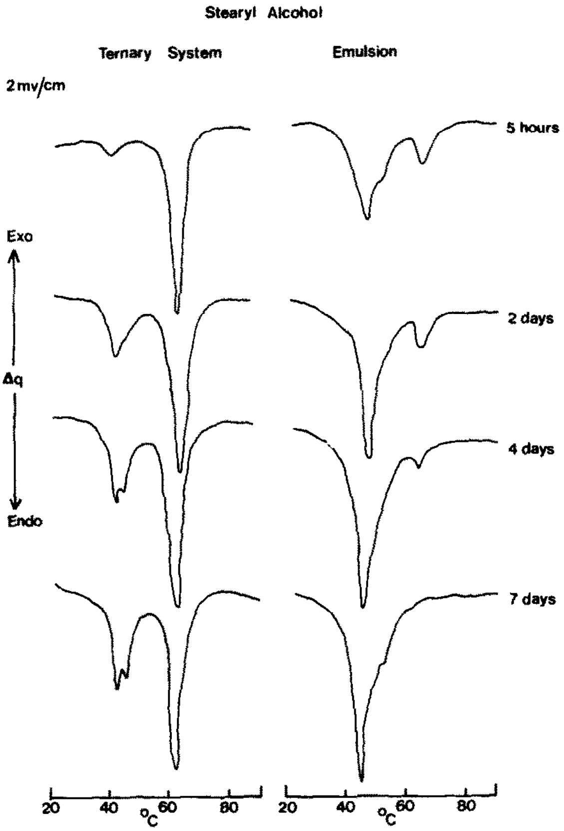

Fig. 6. Pure stearyl alcohol ternary system and emulsion. D.S.C. data after storage at 25°C for stated times.

solution at 70°C, and then cooling rapidly whilst mixing to the storage temperature (25°C). At high temperature, the fatty alcohol interacts with aqueous cetrimide solution to form smectic liquid crystals. As the system cools to below T_{pen} (the hydrocarbon chain melting temperature) interaction diminishes and the liquid crystals precipitate to form a complex viscoelastic ternary phase.

The oil-in-water creams were prepared in a similar manner to the ternary systems, with the modification that the alcohol is dissolved in liquid paraffin. At high temperature, excess alcohol diffuses into the continuous phase and interacts with surfactant solution to form liquid crystals. A small portion of the oil also solubilizes. As the cream cools to below T_{pen}, the liquid crystals precipitate to form a viscoelastic continuous phase. This continuous phase is responsible for the appearance and rheological properties of the emulsion (Barry and Eccleston, 1973).

The results of the D.S.C. experiments showed that with pure fatty alcohols, emulsion instability was caused by phase transitions in the continuous phases. They imply that such ternary emulsion continuous phases can exist in several forms, each stable over a definite temperature range. The phase that is stable at the storage temperature depends on alcohol chain length and homologue composition.

Pure long-chain alcohols can exist in at least three solid polymorphic modifications. The high temperature α-form separates first from the melt and is stable over a narrow temperature range. In this form, the hydrocarbon chains are orientated with their long axes at right angles to the layer planes, and rotate about these axes. In the β-form the hydrocarbon chains are non-rotating and in the γ-form they are tilted toward the layer plane. The γ-polymorph exists only in even members of higher alcohols and is the stable form in alcohols of chain lengths greater than C_{20}. With hexadecanol and octadecanol as used in this work the β- and γ-polymorphs can co-exist, although the β-form is usually in excess (Tanaka et al., 1958).

The D.S.C. data for the alcohols (Fig. 3) in this work correlated with the literature (Junginger, 1980). The broad endotherms peaking at 52°C (range 46–58°C) for cetyl and 62°C (range 57–68°C) for stearyl alcohol incorporate the β (and γ)–α-transitions and the melting of the α-form. With cetostearyl alcohol containing a mixture of homologues, the transition temperatures are lowered and polymorphic ranges extended (Stewart, 1960; Fukushima et al., 1977) so that the γ–α transition occurs as a weak peak at ~ 30°C, the β–α transition as a broad endotherm over the temperature range 34–45°C, and the sharp endotherm peaking at 55°C is due to the melting of the α-polymorph.

In water fatty alcohols exhibit limited swelling to form crystalline hydrates and transition temperatures are depressed even further. The thickness of the water layers in the hydrates is limited by the considerable strength of the Van der Waals' forces between the lipid layers which balance osmotic repulsions. Similar polymorphic behaviour is shown by other amphiphiles and lipids.

In addition to these well-documented forms a limited number of amphiphiles, usually of mixed homologue composition (e.g. phospholipids, monoglycerides) when cooled in water can form lamellar crystalline gel-like phases under certain conditions, e.g. when ionic groups are present, instead of precipitating out to form coagel phases (hydrated crystals and water (Krog and Lauridson, 1976; Hauser, 1984)). These bilayer gel phases, which are greatly swollen with water, can coexist with α-crystals. Krog and Borup (1973) showed that either by adding small amounts of ionic surfactant to a monoglyceride in water, or by neutralizing the free fatty acids with NaOH, repulsive forces were increased so that swelling could continue in principle to infinite dilution in excess water.

It must be emphasized that these gel phases occur at temperatures below the melting temperature of the hydrocarbon chains (i.e. T_{pen}). The bilayers probably consist of stiff, rotating alkyl chains (α-modification) separated by thick layers of water. They should not be confused with the lyotropic and thermotropic liquid crystalline phases that occur above the chain-melting transition and are extensively documented in the literature. In these, there is much greater chain mobility, although they may also swell in the presence of ions (Krog and Lauridsen, 1976; Rydhag, 1979; Rydhag and Wilton, 1981).

Cetostearyl alcohol in the presence of cetrimide and excess water (> 90% water) can also swell to form crystalline gel phases. The swelling process can be observed microscopically at room temperature (20–25°C); at higher temperatures (above the hydrocarbon chain melting temperature) smectic liquid crystals are visible (Barry and Eccleston, 1973; Eccleston, 1982). A recent low angle X-ray diffraction study of a stable cream prepared with an anionic emulsifying wax confirmed that a "swollen" gel phase was an important component of the cream (Junginger, 1984).

When these data are considered collectively, and compared with the results of this work then a possible explanation for the phase transitions responsible for emulsion instability emerges. The stable cetostearyl alcohol ternary system is a multiphase system composed of α-crystalline hydrates of cetostearyl alcohol, swollen bilayer gel phase of cetostearyl alcohol containing solubilized cetrimide, and free water. In the emulsion, an additional oil phase is present. In these stable, semisolid cetostearyl alcohol systems the mixture of chain lengths of the alcohol, and the solubilization of the cetrimide (also a mixture of homologues) created sufficient disorder and inhibited crystallization so that the viscoelastic gel phase is stable over a wide temperature range existing down to and below room temperature.

The broad endotherm in the cetostearyl alcohol systems starting close to 45°C and peaking at approximately 63°C represents the viscoelastic gel network–liquid crystalline transition. This starting temperature correlates well with the chain melting temperature (~ 45°C) obtained with microscopic diffusion experiments (Barry and Eccleston, 1973). The asymmetric endotherm starting at approximately 14°C probably represents the γ and β–α crystal transitions. As the temperature increases to the chain melting temperature, excess water is continually interpositioned between the bilayers causing further swelling to form additional gel phase. This leads to an increase in consistency as temperature rises to the chain melting temperature (Barry and Saunders, 1970b).

In contrast, in systems prepared with pure alcohols, the viscoelastic phase that formed initially from the heating, cooling and mixing cycle of preparation was metastable at storage temperature. Thus on storage, the lamellar double layers of the gel phase approach one another, reducing the amount of interlamellar water and at the same time there is probably a polymorphic transition from the α-configuration to the more stable β- or γ-forms. Thus the viscoelastic gel phase gradually separates into hydrated crystals and crystalline adducts of surfactant and alcohol, dispersed in free water.

As the network entrapping the oil globules disintegrates, emulsions thin and droplet coalescence occurs with eventual oil–water separation. Crystalline adduct formation is favoured with pure amphiphiles with small polar groups and straight hydrocarbon chains of equal lengths. This allows for close packing between the amphiphile and surfactant molecules (Goddard and Kung, 1965; Kung and Goddard, 1965). In unstable systems, the broad low temperature endotherm that develops on storage possibly represents the β–α transition and the high temperature endotherm, sometimes resolved as a doublet may represent distinct α-gel and gel–liquid crystalline transitions.

Microscopic diffusion experiments support the view that these gel phases are thermodynamically unstable at room temperature. There was little microscopic interaction or swelling at room temperature between pure alcohols and cetrimide in excess water, although liquid crystals did form at high temperature (Eccleston, 1977).

Conclusions

Liquid paraffin-in-water emulsions prepared with cetrimide and alcohols cetostearyl, cetyl and stearyl, and ternary systems formed by dispersing cetrimide and each fatty alcohol in water were examined as they aged using rheological and D.S.C. echniques.

The similarities between the rheological and D.S.C. results for each ternary system and its corresponding emulsion throughout the testing period support the view that each ternary system is structurally similar to the continuous phase of the corresponding emulsion.

The cetostearyl alcohol ternary system and emulsion were stable semisolids. D.S.C. curves were relatively simple, and data did not change over the 30-day storage time. The crystal–gel network transition (~ 14°C) and the gel network–liquid crystalline transitions (~ 45°C) are identified and indicate that at storage and testing temperature (25°C) the viscoelastic gel network phase is stable.

In contrast, systems prepared from pure alcohols, although initially semisolid, broke down on storage to become mobile liquids. As pure alcohol systems aged, apparent viscosities reduced, and D.S.C. data changed to show that the crystel–gel network and the gel network–liquid crystalline transitions were well above 25°C.

The results indicate that emulsion continuous phases, formed from the interaction of cetrimide and fatty alcohol in water, can exist in several forms, each stable over a definite temperature range depending on alcohol chain length and homologue composition. A stable emulsion is produced only when one of these, the viscoelastic gel phase, is stable at storage temperature.

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