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MICROSTRUCTURAL CHANGES DURING THE STORAGE OF SYSTEMS CONTAINING CETOSTEARYL ALCOHOL/POLYOXYETHYLENE ALKYL ETHER SURFACTANTS

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ABSTRACT

Non-ionic emulsifying wax/water ternary systems composed of water, cetostearyl alcohol and non-ionic polyoxyethylene alkyl ether surfactants ($R-(OCH_2CH_2)_AOH$ with polyoxyethylene (POE) chain lengths, A, varying from 10-30 and R = cetostearyl were examined as they aged for several weeks. The techniques employed included rheological (Ferranti-Shirley cone and plate viscometer), microscopical (brightfield and between crossed polars), thermal (thermogravimetry and D.S.C) and ultracentrifugation.

The rheological properties of the samples were complex. They confirmed, however, that all ternary systems increased in consistency on storage. For each ternary system apparent viscosities (ηapp) increased as the samples aged. In addition, ternary systems prepared with surfactants with long POE chains were generally of a higher consistency than similar ternary systems containing shorter POE chains.

Each ternary system was considered to be composed of crystalline and gel (L_β) phases dispersed in bulk (free) water. The overall consistency of each system was related to the swelling ability and the relative amounts of gel phase present; this in turn depended on the POE chain length of the surfactant. The structural changes on storage were due to the formation of additional gel phase. This occurred because hydration of POE chains to form gel phase was limited at the high temperature of manufacture. On storage at lower temperature (25°) the increased solubility of the POE chains allowed additional gel phase to form. However, this now occurred relatively slowly because of the crystalline nature of the hydrocarbon chains. Microscopical observations support this theory, for the timescale of observed interaction correlated well with the consistency and 'free' water changes on storage.

INTRODUCTION

Many dermatological emulsions are formulated using mixed emulsifiers of the surfactant/fatty alcohol type (emulsifying waxes). The surfactants may be ionic or non-ionic, although in general non-ionics are preferred, because they are less irritant to the skin and exhibit fewer incompatibilities with charged drugs and excipients than the ionics. Microstructural differences between ionic and non-ionic preparations are not always recognised. However, oil-in-water creams stabilised by such mixed emulsifiers are not simple two phase oil and water emulsions, but multicomponent systems containing additional aqueous (e.g. lamellar liquid crystalline or gel) phases. These additional phases form when emulsifier, in excess of that necessary to form a monomolecular film at the oil droplet/water interface, interacts with water. The phase behaviour of a variety of ionic and non-ionic mixed emulsifier/water systems, and their relevance to cream microstructures have been the subject of recent reviews (1-3).

A major disadvantage of using non-ionic emulsifying waxes is that the resultant o/w creams and lotions often gel-up after manufacture. This may result in a product which has unpredictable properties on storage, i.e. becomes so thick that it is unacceptable cosmetically or that drug bioavailability is altered. Rheological investigations into structural build-up showed that whereas ionic lotions and creams reached their normal semi-solid consistencies within a few hours of preparation, the consistencies of systems prepared with non-ionic emulsifying waxes increase considerably on extended storage (4-6). Moreover, analysis of viscoelastic data clearly indicated that both the mechanism by which non-ionic and ionic preparations form and their final microstructures differ considerably (4,7).

The present paper reports an investigation into such structural changes on storage, and is part of an overall investigation into the microstructures of complex pharmaceutical emulsions and the influence of drugs on them. For this work ternary systems, formed by mixing similar concentrations of mixed emulsifier in water to those used in commercial creams, were examined. Such ternary systems have been shown to be suitable models to study the structures of emulsion continuous phases (1,2). The systems were prepared with a series of surfactants of increasing HLB numbers with polyoxyethylene chain lengths varying from 10-30.

MATERIALS AND METHODS

Materials

Water was double distilled and de-ionised. Cetostearyl alcohol B.P. (Evans, UK) and non-ionic surfactants of the polyoxyethylene alkyl ether type $(CH_3(CH_2)_XCH_2-(OCH_2CH_2)_AOH$ where X = 14 or 16 and A varied from 10 to 30 (Texofor A series, A.B.M. Chemicals, UK) were used as received. In the text individual surfactants are abbreviated as A10, A14, A18, A30 and A1P where the numbers denote the ethylene

TABLE I

Composition of ternary systems (g)

	T,A10	T,A14	T,A18	T,A1P	T,A30
Surfactant*	3.6	4.6	5.5	6.4	8.2
C/S Alcohol	25.6	25.6	25.6	25.6	25.6
Water	300.0	300.0	300.0	300.0	300.0

* For each ternary system T, AX, X represents the surfactant polyoxyethylene chain length

oxide chain length and A1P represents Cetomacrogol 1000 BPC (A = 20-24).

Preparation of Ternary Systems

Ternary systems were prepared according to the formulae in Table 1 by a standardised procedure that involved melting the cetostearyl alcohol and surfactant together and adding water (which had been previously boiled to remove air) at approximately the same temperature (80°C), then cooling slowly whilst mixing with a Silverson homogeniser. The homogeniser speed was controlled throughout to avoid incorporation of air.

The molar ratios of each polyoxyethylene (POE) alkyl ether surfactant to cetostearyl alcohol (1:25) and the total concentration of each mixed emulsifier in water (10%) were chosen because with Cetomacrogol 1000 this molar ratio and concentration produces systems of the soft semisolid consistency used commecially. Samples were stored at 25°C.

Microscopy

Each ternary system was examined using the Polyvar microscope (Rheichart-Jung, Austria) in brightfield and between crossed polars. The systems were examined immediately after preparation and at frequent intervals over a one month storage period.

Rheology

Rheological experiments were performed at 25°C using a Ferranti-Shirley cone and plate viscometer in automatic mode with a sweep time of 600 seconds. The maximum shear rate was 1684 sec^{-1} and the resultant flow curves were displayed on an X-Y plotter. Samples were tested immediately after preparation and frequently over one month's storage.

Thermogravimetric Analysis

The ratio of free and interlamellarly bound water was determined as systems aged using the thermogravimetric method described by De Vringer et al (8). This involves recording the weight loss at 2°C/minute (Stanton-Redcroft TG 750, UK) when about 4mg of each ternary system was heated from ambient temperature to approximately 80°C, (i.e. when no further weight loss was registered).

Ultracentrifugation

Samples were ultracentrifuged (MSE Superspeed 75, MSE, UK) at 25°C for times ranging from three to twenty hours at 130,000g and the quantity of free water determined by weighing the water that separated.

Differential Scanning Calorimetry (D.S.C.)

Preliminary D.S.C. experiments between ambient and +100°C were performed on systems aged for about two months using the Mettler DSC 30 system (Mettler, Switzerland).

RESULTS

Appearance of Systems

Sample T,A10 was a white, mobile lotion immediately after preparation and although some thickening was visible it remained mobile on storage. All other samples were semi-solids.

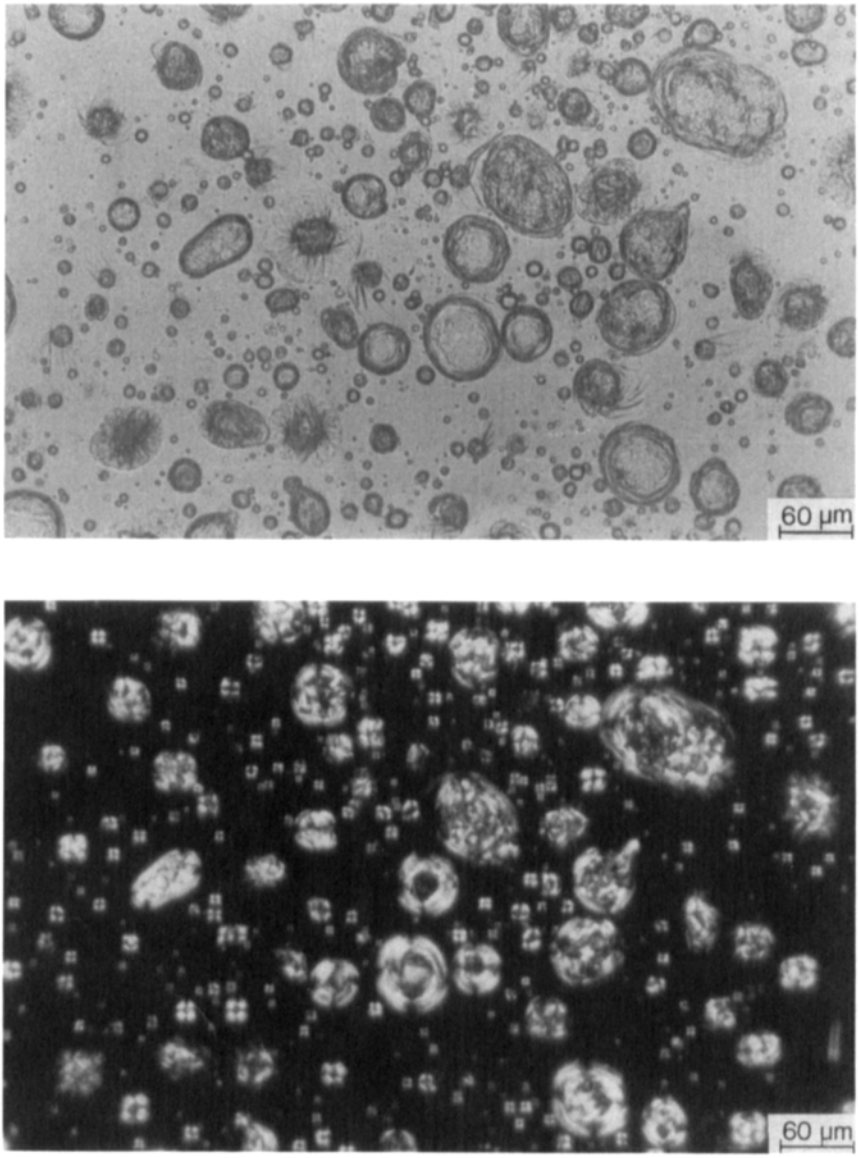

FIGURE 1
Representative photomicrographs of freshly prepared ternary systems in brightfield and between crossed polars. (a) and (b) = T,A10; (c) and (d) = T,A14; (e) and (f) = T,A1P.

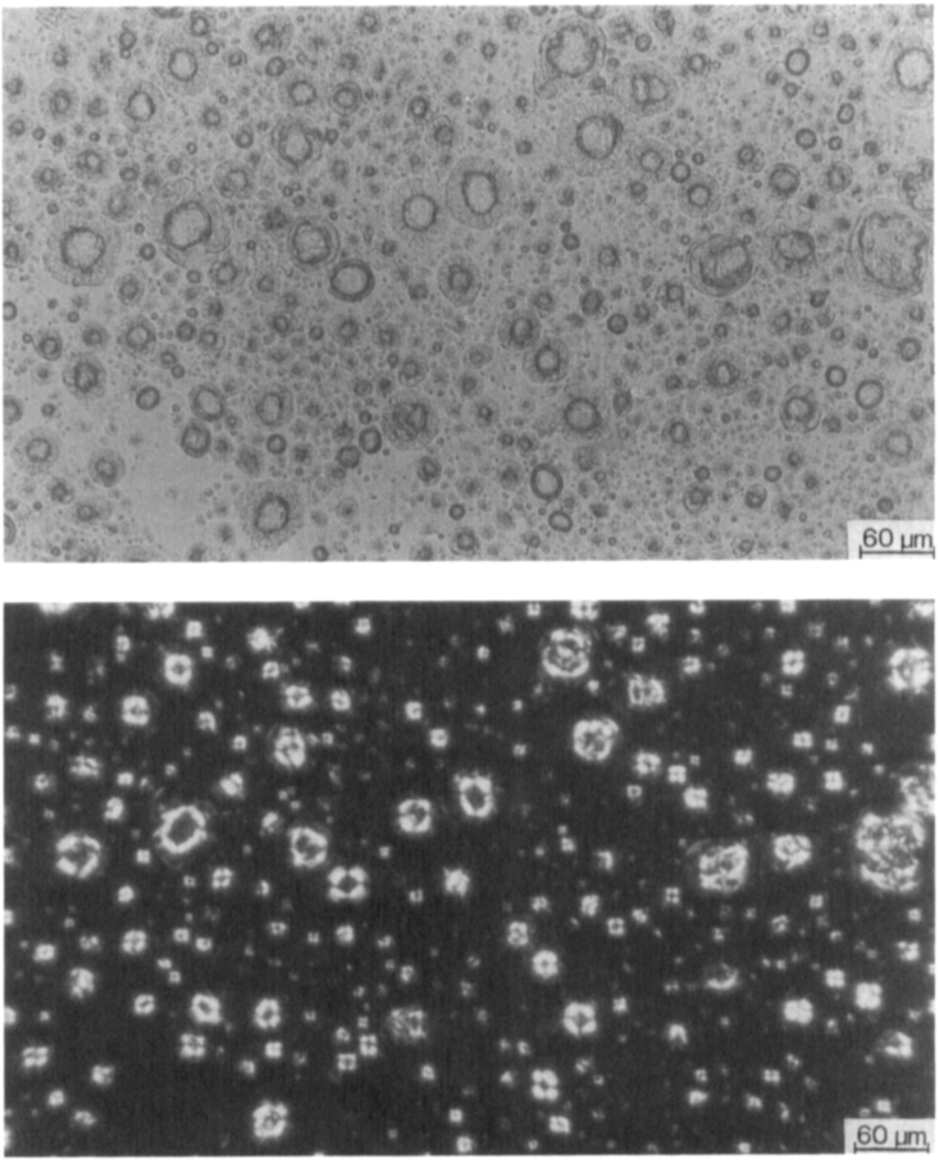

FIG. 1 CONTINUED

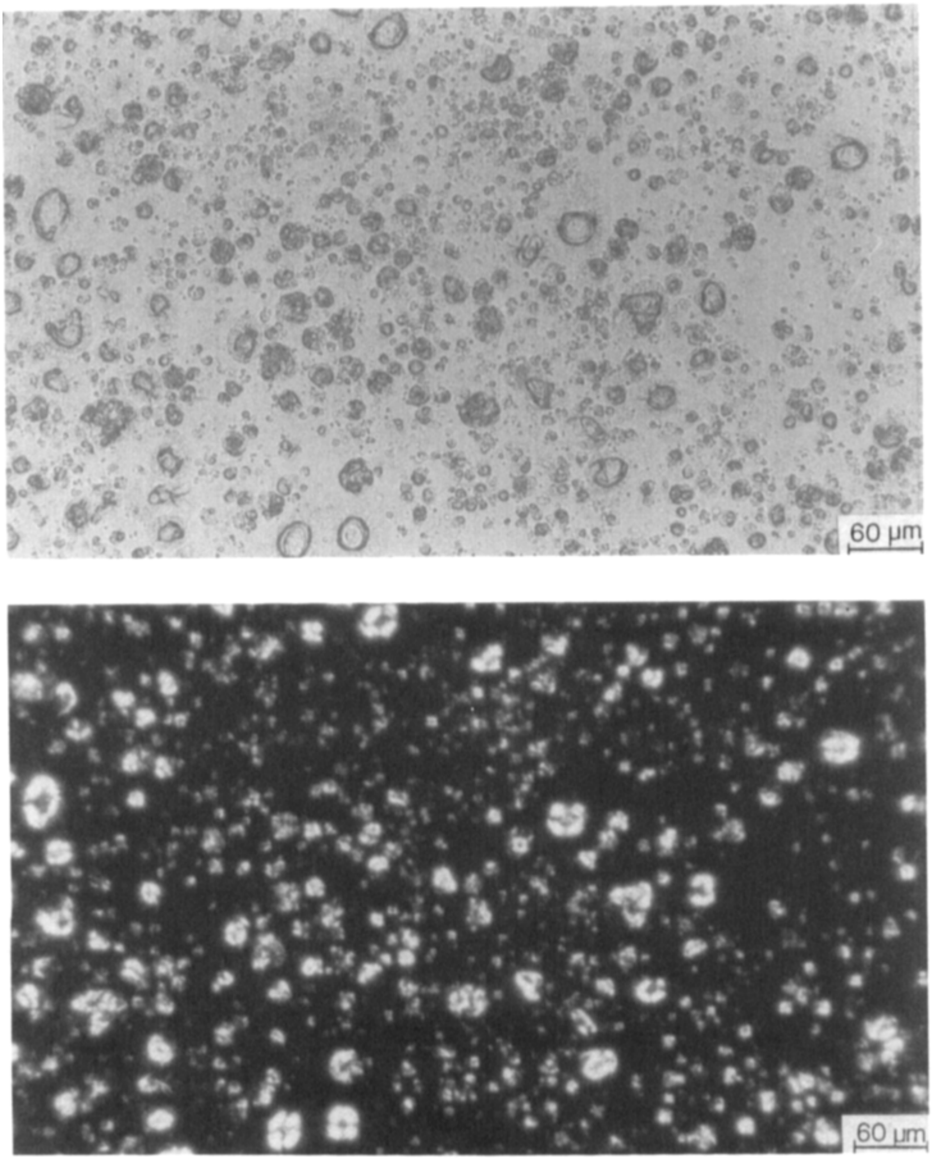

FIG. 1 CONTINUED

Microscopy

Representative photomicrographs of freshly prepared systems are shown in Figure 1. In ordinary light, all ternary systems contained large masses of partially interacted emulsifying wax in addition to many smaller particles. The smaller particles which appeared as distorted maltese crosses in polarised light, were present in fresh and aged systems. The partially interacted emulsifying wax was most prominant in T,A10, where large (often greater than 50μm) dense masses of material with ciliated structures radiating from them, were apparent (Fig. 1a). These unreacted masses were smaller in ternary systems prepared with surfactants of longer POE chain lengths. For example, there were large numbers of particle sizes of up to 40μm in system T,A14, but most were less than 25μm in system T,A1P.

On extended storage, further interaction occurred and these structures had either disappeared altogether as in high POE systems, or had changed and reduced in size (low POE number system). In those masses remaining, mainly orientated 'onion ring' structures rather than cilia, surrounded the central mass (cf. Figs. 1a, b & c).

Rheology

The flow curves obtained for all the samples were complex. Representative plots are shown in Figure 2. Immediately after preparation samples T,A10 and T,A14 showed clockwise hysteresis loops and sometimes the up and down curves crossed over, implying that the shearing cycle itself causes some structural build-up. In aged samples, the flow curves reverted to the more usual anticlockwise hysteresis loops. The flow curves for the other systems (T,A18; T,A1P; T,A30) also changed after storage.

All ternary systems showed increases in apparent viscosities on storage but at different rates and to different extents (Fig. 3). For clarity, ηapp's for initial and one month systems are shown in Table 2.

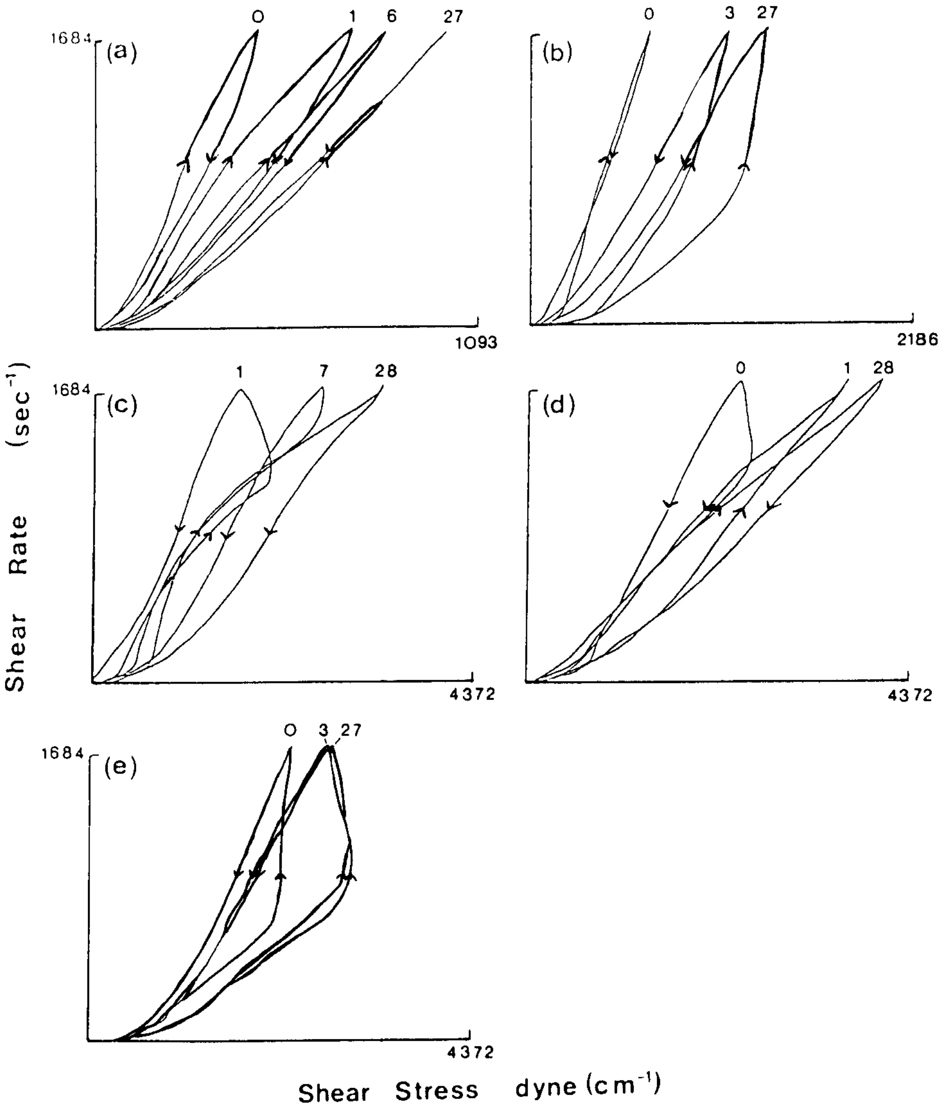

FIGURE 2

Ferranti-Shirley cone and plate viscometer. Representative flow curves for ternary systems (a) T,A10; (b) T,A14; (c) T,A18; (d) T,A1P and (e) T,A30, aged for the stated times (days).

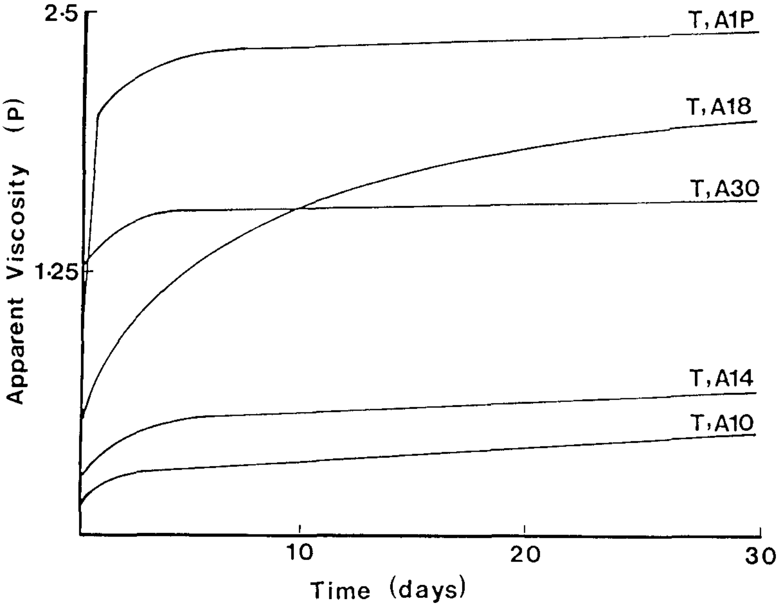

FIGURE 3
The variation of apparent viscosity at the loop apex, η_{app}, (Poise) for each ternary system with storage time (days).

TABLE 2

Apparent Viscosities at the loop apex, η_{app} (Poise) immediately after preparation and after one month's storage

	T,A10	T,A14	T,A18	T,A1P	T,A30
0 Hours	0.30	0.39	0.74	1.02	1.36
1 Month	0.62	0.80	1.93	2.40	1.61

Systems prepared with shorter POE chain length surfactants are generally of a lower consistency, and show less structural build up than those containing longer POE chain lengths (cf. Table 2, Figures 2 and 3). It was noted that although T,A30 was a highly structured semisolid, showing changes on storage, its apparent viscosities were not as high as those expected from the general trend of increasing napp increase with increasing POE chain length and its final consistency was lower than ternary systems T,A18 and T,A1P.

Ultracentrifugation

All the ternary systems separated into two layers after centrifugation. The top layer was a thick, white semisolid and was composed mainly of distorted spherulites and crystalline material; the crystal masses appeared to have interacted further during centrifugation. The percentage of free water was calculated from the weight of water that separated as the bottom layer. Results obtained were erratic and are discussed later.

Thermogravimetric Analysis

Figure 4 shows typical thermogravimetric curves for T,A30. Similar data were obtained for the other ternary systems throughout the storage cycle. In each ternary system there were two inflexions in the weight loss curve; the first peaking at 43°C and ending at 46-48°C and the second peaking at 55°C and ending at 62-63°C. In general, free water decreased both as samples aged and as the number of POE groups in the surfactant increased Figure 5, although values were again rather erratic.

Differential Scanning Calorimetry

DSC thermograms for aged systems were obtained. In all systems a broad endotherm starting about 50°C and peaking at 60°C was obtained (Figure 6). The enthalpies were all approximately 11J/g. This represented the melting enthalpies of the hydrocarbon chains of the mixed emulsifier.

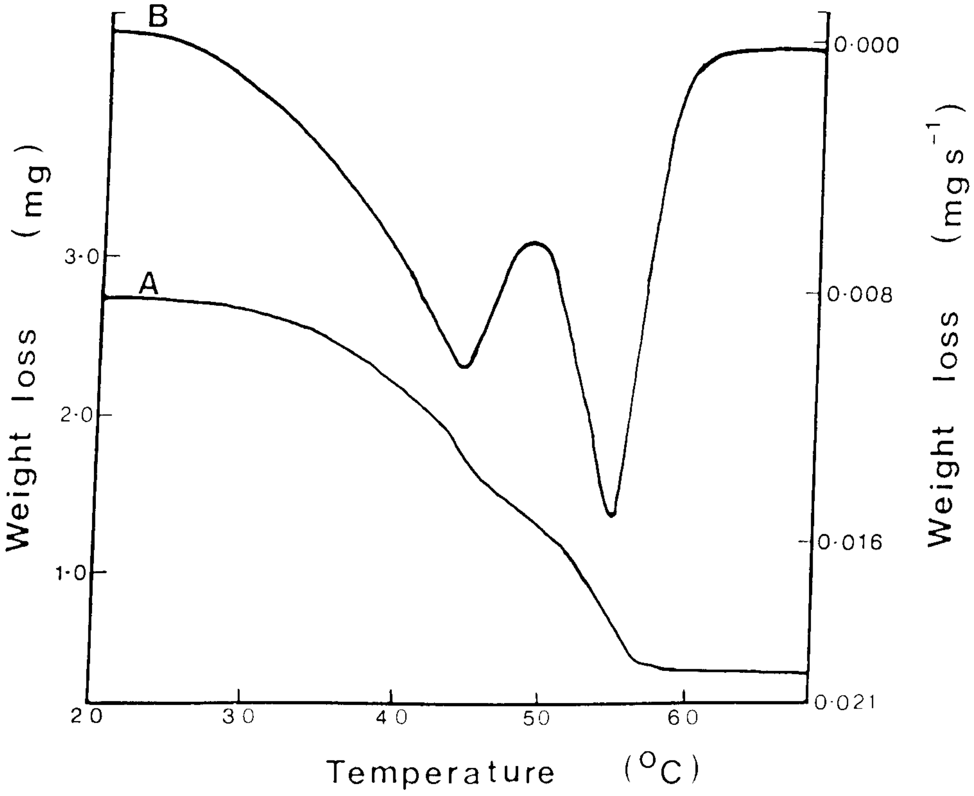

FIGURE 4
Typical thermogravimetric, A (mg) and differential thermogravimetric, B (mg sec^{-1}) curves showing the stages of water loss (T,A30).

DISCUSSION

Each ternary system is a multiphase system composed of hydrated crystalline cetostearyl alcohol and gel (L_β) phase dispersed in 'free' water. The gel phase consists essentially of crystalline hydrocarbon bilayers of alcohol and surfactant, separated by aqueous layers containing hydrated polyoxyethylene groups of the surfactant (2,9,10). Microscopically, this phase is visible as large (often several μm, cf, Figure 1) multilamellar

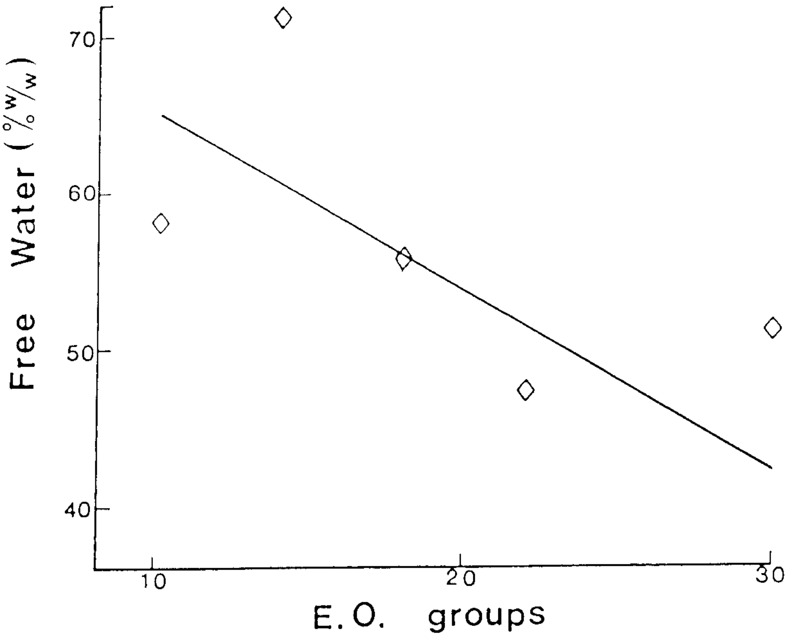

FIGURE 5
Variation of % free water (w/w) with the number of surfactant ethylene oxide groups for ternary systems aged for one month.

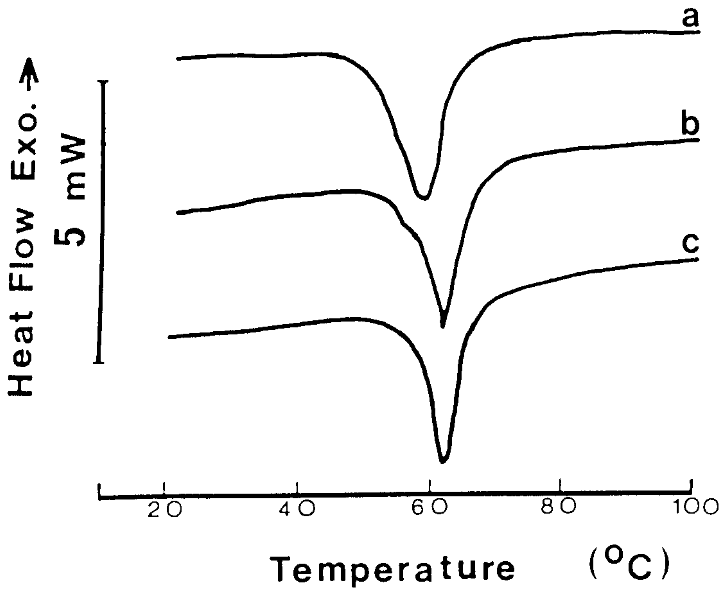

FIGURE 6
D.S.C. data for ternary systems (a) T,A10; (b) T,A14 and (c) T,A1P, aged for two months.

vesicles which show rather distorted extinction crosses in polarised light. Although fatty alcohol alone can only exhibit limited swelling to form crystalline hydrates, fatty alcohol/surfactant gel phases can swell to a much greater amount (2,3).

Structural changes in each sample were represented by apparent viscosity values (ηapp) calculated at the apex of each hysteresis loop. Although such values should be treated with caution as they are not fundamental rheological parameters, they have been shown in the past to be useful guides of consistency in closely related systems, as long as they are also correlated with visual observation of flow curve changes. The rheological data confirmed that all ternary systems increased in consistency on storage and that the extent and time scale of these increases were related to the number of POE groups present in the surfactant. The structural changes were usually accompanied by reductions in the amount of free water. In addition, systems containing surfactants of high POE number contained less free water and were thicker than those containing shorter POE chains.

The techniques (ultracentrifugation and thermogravimetric) used to investigate the relative amounts of free and 'bound' water in each ternary system were not satisfactory. Although thermogravimetric results appeared to somewhat correlate with rheological data, in that systems of high consistency generally contained less free water, ultracentrifugation data were completely erratic, and no discernable trends were observed. Similar inconsistencies were observed by Rowe and Bray (11) in ultracentrifugation results for ionic emulsions. Water evaporation during preparation of the systems does not completely explain the grossly erratic results, nor does the fact that the consistency of each system will itself be increasing as water separates during centrifugation. It is possible that with these systems the strong forces experienced during centrifugation cause additional structural changes. Microscopical examinations of the system both before and after centrifugation implied that crystalline masses had further interacted. The inconsistencies in thermogravimetric data were due to the fact that evaporation of these systems is a very complex phenomenon, possibly involving simultaneous dehydration of POE groups as well as evaporation of bulk water.

When these results are correlated with microscopical examinations, they imply firstly, that the overall consistency of each ternary system is related to the swelling ability and the amount of gel phase present, and secondly that the amount of gel phase relative to the other phases depends on the polyoxyethylene chain length of the surfactant.

Each ternary system was prepared by mixing molten alcohol and surfactant with water at high temperature, and then cooling whilst still mixing to the storage and testing temperature (25°C). A very complex phase situation is envisaged during this preparation procedure because hydration of the polyoxyethylene chains although limited at the high temperature, is continually increasing as the systems cool to the storage temperature. Above the hydrocarbon chain melting temperatures, mixed lamellar liquid crystalline and micellar phases are present as well as relatively large masses of molten alcohol and surfactant. In these masses the hydrocarbon chains of the surfactant are dispersed amongst those of the alcohol and the POE groups are present both at the surface and clustered within the masses.

As systems cool and the POE regions become more soluble, water penetrates into the masses and, if the hydration forces are strong enough lamellar liquid crystals will separate. When the hydrocarbon chain crystallization temperature is reached (approx. 50°C cf. D.S.C. data), the liquid crystals transform to gel phase, and the partially hydrated emulsifying wax precipitates (cf. Figure 1). On storage, water continues to penetrate into the crystalline masses to further hydrate the POE regions, and additional gel phase forms. This occurs relatively slowly, because of the crystalline nature of the hydrocarbon chains causing water penetration and rearrangement into swollen gel bilayers to be extremely slow. As additional gel phase forms on storage, the amount of free water is reduced and the ternary systems thicken.

The tendency of gel phase to separate from the crystalline masses and the thickness of the interlamellar water layers in this phase will depend on the net repulsive forces caused by hydration. The nature of hydration forces have been discussed recently for polyoxyethylene alkyl ethers containing both short (<10) and long (up to 30) POE chains (12-15). The so-called interlamellar or 'bound' water is considered to include all the arrangements of water molecules relative to the polyoxyethylene chains including hydrogen bonding, dipole interactions and water that is physically trapped both within and between the POE chains.

In ternary systems prepared with surfactants of short ethylene oxide chain length, especially T,A10, the hydration forces are not sufficient to force the hydrocarbon chains of the emulsifying wax crystals apart for significant quantities of additional gel phase to form on storage. Thus partially hydrated emulsifying wax masses are visible microscopically in both fresh and aged ternary systems T,A10 and T,A14. It was observed that the consistency of these systems had increased when sheared during rheological experiments. It is likely that the shearing forces mechanically disrupt the masses, exposing the surfactant chains to the water, with the formation of the additional gel phase.

As the POE chain length is increased from A10 to A30 hydration forces increase. Although only two molecules of water hydrate each ethylene oxide group by hydrogen bonding, long POE molecules may also trap additional water between the chains (16-19), thus additional gel phase separates from the masses. The thickness of the interlamellar layers will also be greater as POE chain length increases. Microscopically, the crystalline masses reduce in number and are smaller as POE chain length increases. The aged sample T,A30, although semi-solid, is of a lower consistency than expected. This may be because with very long POE chains, increased crowding now prohibits hydration of the surfactant so that the thickness of the interlamellar layers is smaller than expected.

CONCLUSIONS

1. Ternary systems composed of water, cetostearyl alcohol and non-ionic polyoxyethylene alkyl ether surfactants ($R-(OCH_2CH_2)_AOH$ with polyoxyethylene chain length A, varying from 10-30 and R = cetostearyl were examined as they aged using rheological, microscopical, thermal and ultracentrifugation techniques.

2. In general, ternary systems containing surfactants with longer POE chains were of a higher consistency and contained less free water than similar ternary systems prepared with shorter POE chains. In addition, each ternary system showed structural build-up on storage; as consistency increased free water decreased and microscopical changes were visible.

3. Each ternary system is a multiphase system composed of hydrated crystalline cetostearyl alcohol and α-crystalline gel (L_β) phase dispersed in 'free' water. The gel phase consists essentially of crystalline hydrocarbon bilayers of alcohol and surfactant, separated by aqueous layers containing hydrated polyoxyethylene groups of the surfactant. This phase is identified microscopically by characteristic distorted extinction crosses in polarised light.

4. The overall consistency of each ternary system is related to the swelling ability and the amount of gel phase present; this in turn depends on the POE chain length of the surfactant. It is shown that the structural changes on ageing are due to the slow formation of additional gel phase on storage. As fresh gel phase forms, sequestration of free water occurs and the consistency of ternary systems increase. The structural changes occur because hydration of POE chains is limited at the high temperatures of manufacture, but increases continually as systems cool. On storage, the increased solubility of the POE chains causes

additional gel phase to form. This occurs relatively slowly due to the slow rearrangements of crystalline hydrocarbon chains.

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