ELSEVIER

International Journal of Pharmaceutics 203 (2000) 127–139

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Synchrotron X-ray investigations into the lamellar gel phase formed in pharmaceutical creams prepared with cetrimide and fatty alcohols

G.M. Eccleston[a],*, M.K. Behan-Martin[a], G.R. Jones[b], E. Towns-Andrews[b]

[a] *Department of Pharmaceutical Sciences, University of Strathclyde, 24 George Street, Glasgow G41 5EU, UK*
[b] *Daresbury Laboratory, Warrington WA4 4AD, UK*

Received 16 March 2000; accepted 3 May 2000

Abstract

Semisolid liquid paraffin-in-water emulsions (aqueous creams) prepared from cetrimide/fatty alcohol mixed emulsifiers, and ternary systems formed by dispersing the mixed emulsifier in controlled percentages of water were examined as they aged using a combination of low and high angle X-ray diffraction measurements (Daresbury Laboratory Synchrotron Radiation Source). The results were correlated with the rheological properties measured in earlier studies. The cationic emulsifying wax showed phenomenal swelling in water. The reflection that incorporates interlamellar water increased continuously from 74 Å at 28% water to over 500 Å at 93% water. The trend was not influenced by the method of incorporation of the components and swollen lamellar phase was also identified in the corresponding emulsion. The swelling, which was due to electrostatic repulsion, was suppressed by salt and was reduced when the surfactant counterion was changed from Br^- to Cl^-. Changes in rheological properties on storage and in the presence of salt were correlated with changes in water layer thickness. High angle diffraction confirmed that the hydrocarbon bilayers were in the hexagonal α-crystalline mode of packing. Ternary systems and creams prepared from pure alcohols, although initially semisolid, were rheologically unstable and broke down. Low angle X-ray study into the kinetics of structure breakdown showed that the swollen lamellar gel phase formed initially swells even further on storage before separating. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Pharmaceutical cream; Cetrimide/cetostearyl alcohol ternary system; Lamellar phase; Emulsifying wax; Synchrotron radiation; X-ray diffraction

---

1. Introduction

Oil-in-water emulsions, stabilised by combinations of sparingly soluble long chain fatty alcohols and ionic or non-ionic surfactants, are widely used as vehicles for the delivery of drugs and cosmetic agents to the skin. The emulsifier com-

---

* Corresponding author. Tel.: +44-141-5482510; fax: +44-141-5526443.

E-mail address: g.m.eccleston@strath.ac.uk (G.M. Eccleston).

PII: S0378-5173(00)00447-6

ponents may be added separately during the high temperatures of preparation, or alternatively as a previously blended emulsifying wax. The popularity of such emulsifying waxes in pharmacy and medicine is based on the fact that kinetically stable emulsions, ranging in consistency from mobile lotions at low emulsifier concentrations to semisolid creams at higher concentrations, can be produced. An understanding of the mechanisms by which such mixed emulsifiers modify the rheology of dermatological lotions and creams (self-bodying action) is essential to optimise manufacturing techniques, provide cosmetic elegance and evaluate stability in the presence of drugs and other excipients.

Over the years the gel network theory of emulsion stability has evolved which related the stability and rheological properties of such lotions and creams to the formation of viscoelastic gel networks in their continuous phases. The viscoelastic continuous phase forms when emulsifier, in excess of that required to give a monomolecular film at the oil droplet water interface, interacts with continuous phase water (Barry, 1968; Barry and Eccleston, 1973a; Eccleston, 1986, 1990, 1997). Thus, the physical properties and phase behaviour of the appropriate concentrations of surfactant and fatty alcohol in water (ternary systems) have been widely investigated as structural models for the continuous phases of lotions and creams. The physical chemical techniques employed to characterise the network phases include light and electron microscopy (Barry and Saunders, 1970a; Patel et al., 1985; Rowe and McMahon, 1987), continuous shear and viscoelastic rheology (Barry and Eccleston, 1973b,c; Barry, 1974) differential scanning calorimetry and thermogravimetric analysis (Fukushima et al., 1977; Junginger, 1984; Eccleston, 1985), NMR (Griffiths et al., 1992) and conductivity and dielectric analyses (Rowe and Patel, 1985; Hill et al., 1990; Tamburic et al., 1996; Goggin et al., 1997). The results support the view that specific lamellar phases in which layers of water alternate with emulsifying wax bilayers are an essential component of the gel networks. These lamellar phases may exist in equilibrium with α-crystalline phases and bulk free water.

X-ray diffraction is one of the most direct methods for obtaining information about the swelling behaviour of lipids and surfactants in such bilayer structures. However, measurements made in the past have exhibited shortcomings. For example, X-ray diffraction measurements using the Compact Kratky camera have provided only limited information about these systems. Inherent problems associated with such conventional X-ray sources include their inability to measure the very low scattering angles resulting from low intensity smearing due to the use of slit collimation as well as the long collection times required to produce reasonable statistics. This has meant that published data is generally limited to systems containing less than 70% water (Krog and Borup, 1973; Eccleston, 1974; Junginger, 1984) or to using a simplified lattice model to assess the distribution of water layer thickness (Barry and Rowe, 1989).

This paper reports X-ray investigations into the swelling behaviour of cetrimide based liquid paraffin-in-water creams and ternary cetrimide/fatty alcohol/water systems containing water concentrations of up to 93% using the Synchrotron Radiation Source (SRS) at the Daresbury Laboratory. This source enables the water layer thickness to be measured directly at high water concentrations. The high intensity of X-rays produced by synchrotron radiation and the small beam size (5 × 0.3 mm) result in short data collection times (~ 5 min per sample) and no significant smearing effects in the diffraction range of interest. The detection system at the SRS, consisting of a linear detector and sample to detector distances of up to 6 m, can provide a measurement range of system spacing up to 1000 Å. Cetrimide/fatty alcohol systems were chosen for the study as they have been well characterised and their rheological properties (continuous shear and viscoelastic measurements) have been extensively documented for both stable (cetostearyl alcohol) and unstable (pure alcohol) systems (Barry and Saunders, 1970a,b; Barry and Eccleston, 1973c; Eccleston, 1976). The overall aim was to determine the detailed microstructure of the systems and to relate this to rheological properties and stability.

2. Materials and methods

2.1. Materials

Hexadecanol (99% pure, checked by gas-liquid chromatography (GLC)), cetyltrimethylammonium chloride and cetrimide BP, a homologue mixture of alkyltrimethylammonium bromides (dodecyl 20%, tetradecyl 68% and hexadecyl 10% with trace amounts of other homologues, GLC analysis) was obtained from Aldrich, UK. Cetostearyl alcohol BP, a homologue mixture of cetyl (28%) and stearyl (69%) alcohols with trace amounts of the C12, C14 and C20 alcohols (GLC), liquid paraffin BP and a pre-blended cetrimide emulsifying wax were obtained from Loveridge, UK. Double distilled de-ionised water was used throughout.

2.2. Preparation of systems

Oil-in-water creams (liquid paraffin 20 g, water 300 g, fatty alcohol 25.2 g and cetrimide 2.4 g) and their corresponding ternary systems (water 300 g, fatty alcohol 25.2 g and cetrimide 2.4 g) were prepared from either cetostearyl alcohol or pure cetyl alcohol by mixing the hot excipients at 70°C and then cooling to 25°C whilst mixing. Additional cetostearyl alcohol creams and ternary systems were prepared to the same formulae but incorporating between 0.5 and 2.5% w/w sodium chloride. These ternary systems (containing ~ 93% water) were formulated specifically as structural models for the continuous phases of the creams, and are referred to as model ternary gels in the text to distinguish them from the ternary systems prepared with different amounts of water for the swelling studies (below).

For the swelling studies, a series of mixed emulsifier/water ternary systems (30 g) were prepared with a constant weight ratio of cetrimide to fatty alcohol of 1:9 (approximate molar ratio 1:12) and increasing water percentages of 16.5, 28, 40, 47, 70, 90 and finally 94%, which is similar to the model ternary gel described above. To prepare the systems, the surfactant was added to the required percentage (w/w) of water at 75°C and added to the molten fatty alcohol at the same temperature and then cooled to 25°C whilst stirring. A corresponding series of fatty alcohol/water systems without any surfactant was also prepared in order to aid identification of peaks corresponding to crystalline fatty alcohol.

Additional series of mixed emulsifier/water systems were prepared using (a) the commercial pre-blended cetrimide emulsifying wax, (b) cetyltrimethylammonium chloride instead of cetyltrimethylammonium bromide, and (c) 99% pure hexadecanol instead of mixed homologue cetostearyl alcohol.

2.3. Microscopy

Systems were examined microscopically in brightfield and between crossed polars using the Polyvar microscope (Reichart-Jung, Austria).

2.4. Rheology

Ternary gels and emulsions of similar composition to those used in this study have been extensively examined in the past using both continuous shear and viscoelastic rheology. Thus in this work, selected systems only were examined using a Ferranti-Shirley cone-and-plate viscometer (3.5-cm diameter cone, maximum shear rate 1671 s^{-1} and 600-s sweep time) in conjunction with an automatic flow curve recorder unit to confirm that the systems used in this study showed the same trends reported previously. The influence of electrolyte on rheological properties has not been reported before.

2.5. X-ray diffraction

The X-ray diffraction measurements at high and low angle were performed at the Synchrotron Radiation Source (SRS), Daresbury Laboratory, providing X-rays of wavelength 1.54 Å and brilliance greater than 5×10^{11} photons s^{-1} mm^2 per unit wavelength. Systems were examined at various times over a 12-month storage period and a model ternary gel aged for 3 years was also examined. Low angle measurements were performed either at station 2.1 using a camera length of 6 m or at station 8.2 using a camera length of 3 m and a linear detector to obtain structural information in the region of 25–1000 Å. High angle measurements on selected systems were recorded on film 10 cm from the sample at station 8.2. Ultra small angle scattering (USAX) measurements (scanning system spacings of 2000–20 000 Å) were sometimes used to confirm the presence of first order peaks.

X-ray diffraction provides a simple method of extracting structural information from samples that have strongly contrasting periodicity (Fig. 1). In these systems, scattering intensity maxima are considered as reflections from a series of planes at an angle θ, thus the repeat distances were calculated according to the Bragg equation:

$$n\lambda = 2d \sin \theta \qquad (1)$$

where λ is the wavelength of the incident X-rays (1.54 Å), d is the lamellar spacing (i.e. the sum of the emulsifying wax bilayer and the water layer taken from the centre of one bilayer to the centre of the next) and θ represents the angle of reflection or the Bragg angle. This angle is inversely proportional to the system spacing and the X-ray diffraction data is presented in this paper in reciprocal space, $S(1/\text{Å}) = 2 \sin \theta/\lambda$. Lamellar systems can be easily identified because orders of the main spacing occur in the ratio 1/2, 1/3, 1/4, etc. The diffraction pattern obtained provides detailed information about the bilayer packing and the water layer thickness under different conditions. The lamellar repeat distance d is the sum of the emulsifying wax bilayer distance, d_{ew} and the thickness of the water layer, $d_{\text{aq.}}$ so that

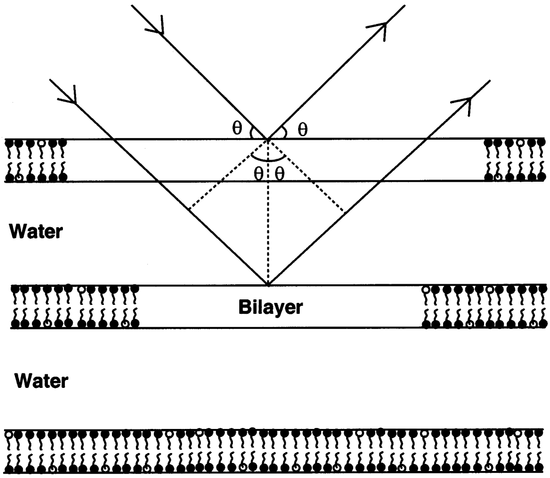

Fig. 1. Schematic diagram of X-ray diffraction from swollen bilayers.

$$d = d_{\text{ew}} + d_{\text{aq.}} \qquad (2)$$

3. Results

3.1. Appearance and microscopy

The mixed emulsifier/water systems were all dry, waxy solids until over 70% water had been added when they became increasingly softer with further addition of water. However, it was not until ~ 90% of water was added that they had the appearance of a viscoelastic cream.

The model ternary gels and the emulsions were shiny, soft, white semisolids when first prepared. On ageing, the stable cetostearyl alcohol creams and ternary gels showed minor increases in consistency and became somewhat less shiny. In contrast, the pure alcohol ternary system and emulsion, although semisolid initially, became mobile on storage and separated into a mixture of crystals and water on extended storage. Fig. 2 shows representative photomicrographs of the cetostearyl alcohol cream and ternary gel (Fig. 2a,b) and the ternary gel formed from pure cetyl alcohol (Fig. 2c) aged for 1 month. The anisotropic structures visible are similar to those reported previously by ourselves and others (Barry and Saunders, 1970a; Fukushima et al., 1977) and are consistent with their known microstructures. In the stable, semisolid cream, remnants of the gel network phase were seen surrounding larger oil droplets and floccules of smaller droplets and anisotropic Maltese crosses indicating lamellar structures were visible in the ternary gel. In contrast, thin platy crystals with an acute angle of ~ 60°, similar to those described as monoclinic cetyl alcohol by Abrahamsson et al. (1960) were clearly visible in the mobile cetyl alcohol ternary gel aged for 1 month.

The cetostearyl alcohol systems prepared with sodium chloride were also unstable and separated

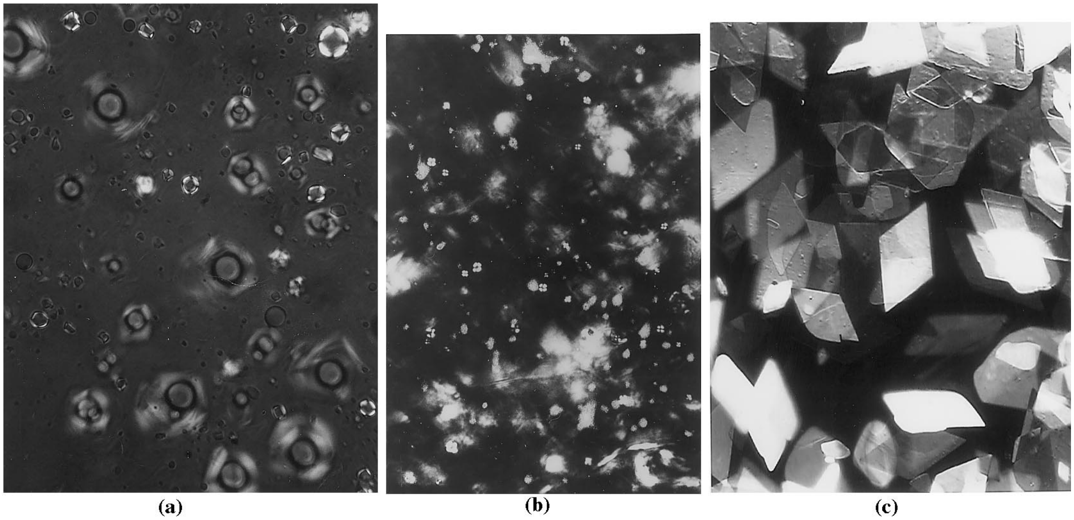

Fig. 2. Photomicrographs of systems aged for 1 month: (a) a cream containing cetrimide/cetostearyl alcohol mixed emulsifier; (b) a model ternary gel (93% water) containing cetrimide/cetostearyl alcohol mixed emulsifier; and (c) a model ternary gel (93% water) containing cetrimide/pure cetyl alcohol.

into two layers, the bottom layer being water and the top layer a white semisolid cream at low electrolyte concentrations and a white fluid at higher electrolyte concentration. The extent of separation was dependent on both storage time and electrolyte concentration. For example, with 0.5% w/w salt, the water layer separated only slowly over ~7 days to ~10% of the total volume. On the other hand, the systems containing 2% w/w NaCl separated within days, with the bottom water layer occupying more than 50% of the total volume. It was not possible to form a cream or ternary gel with greater than 2.5% w/w salt.

3.2. Rheology

Fig. 3 compares flow curves for the cetostearyl alcohol ternary gels aged for 1 day containing increasing amounts of electrolyte. The systems were stirred gently before testing to incorporate any separated water. As the amount of sodium chloride increased, the flow curves reduced in area and moved to lower shear stress values, indicating loss of structure. Similar trends were shown with the creams (not shown). The apparent viscosities calculated at the loop apexes for each salt concentration (w/w, in parenthesis) were 107 mPas (0% salt), 62.6 mPas (1% salt), 43.1 mPas (1.5% salt) and 10.4 mPas (2% salt).

3.3. X-ray diffraction

Cetostearyl alcohol alone in excess water exhibited minimal swelling on hydration (Fig. 4). In the presence of 20% water a sharp diffraction peak was present at 48.8 Å ($1/d$) representing hydrated crystalline bilayers of cetostearyl alcohol, with a second order peak at 24.4 Å. On addition of 40% water the crystalline hydrate swelled to 49.5 Å with the second order at 24.7 Å. At water concentrations above 60% two separate phases formed, a water phase and a cetostearyl alcohol phase which showed a single, sharp diffraction peak at 55.6 Å.

In contrast, when cetrimide/cetostearyl alcohol mixed emulsifier or the pre-blended emulsifying wax was mixed with controlled percentages of water, massive swelling occurred. This is illustrated by the low angle data in Fig. 5, in which four water percentages (28, 47, 70 and 90%, respectively) have been selected to demonstrate successive changes in phase behaviour as the water content was increased to approach that of the model ternary gel (~93% water). For each diffraction profile the diffraction intensity (arbitrary units) was plotted against reciprocal space, $S(1/\text{Å})$ with the orders of the long spacing indicative of lamellar structures.

In the presence of 28% water the diffraction profile of the mixed emulsifier showed four main peaks. Two peaks (labelled lamellar, Fig. 5), represented the first (77 Å), and second order of the lamellar spacing between successive swollen bilayers. There was a broad peak of low intensity at a *d* spacing of ∼55 Å probably due to partially hydrated emulsifying wax bilayers. A sharp peak superimposed on the emulsifying wax bilayer peak, with a *d* spacing of 51 Å, representing hydrated crystalline cetostearyl alcohol.

In the presence of 47% water, the peak due to lamellar separation was centred at 88 Å. The presence of a second order peak indicated that the lamellar spacings were well-defined and abundant. Again, a sharp peak at 51 Å characteristic of crystalline cetostearyl alcohol hydrated with 47% water was obtained. Incorporation of 70% water resulted in the peak arising from the lamellar separation being shifted to considerably larger distances with a mean *d* spacing of 158 ± 12 Å. Second and third orders of this peak again confirmed the presence of a large number of these well-defined structures. Superimposed on the third order peak was the sharp peak at 51 Å due to crystalline cetostearyl alcohol. On incorporation of 90% water the X-ray diffraction profile showed a highly ordered system with even larger lamellar distances of ∼357 Å. The diffraction peak due to this spacing dominated the entire diffraction pattern showing the presence of several orders of the main peak (five in all).

Fig. 6 shows a comparison between low angle data for a model ternary gel (containing ∼93%

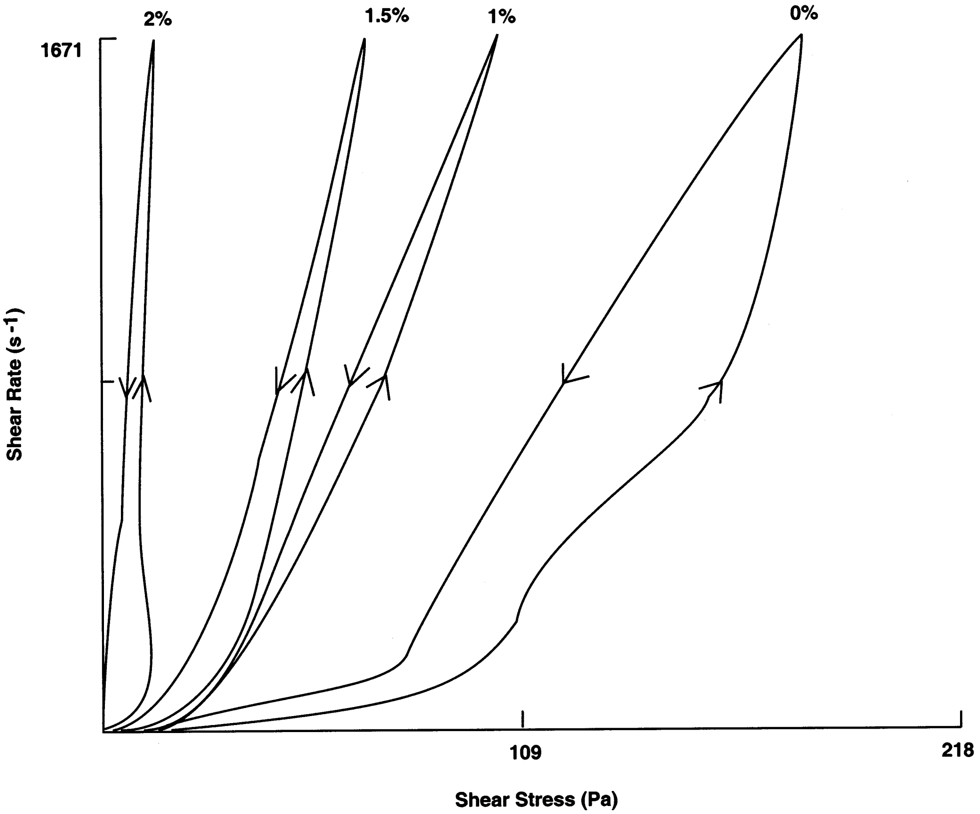

Fig. 3. Ferranti Shirley cone and plate viscometer. The influence of sodium chloride (% w/w) on the flow curves of a model ternary gel is shown.

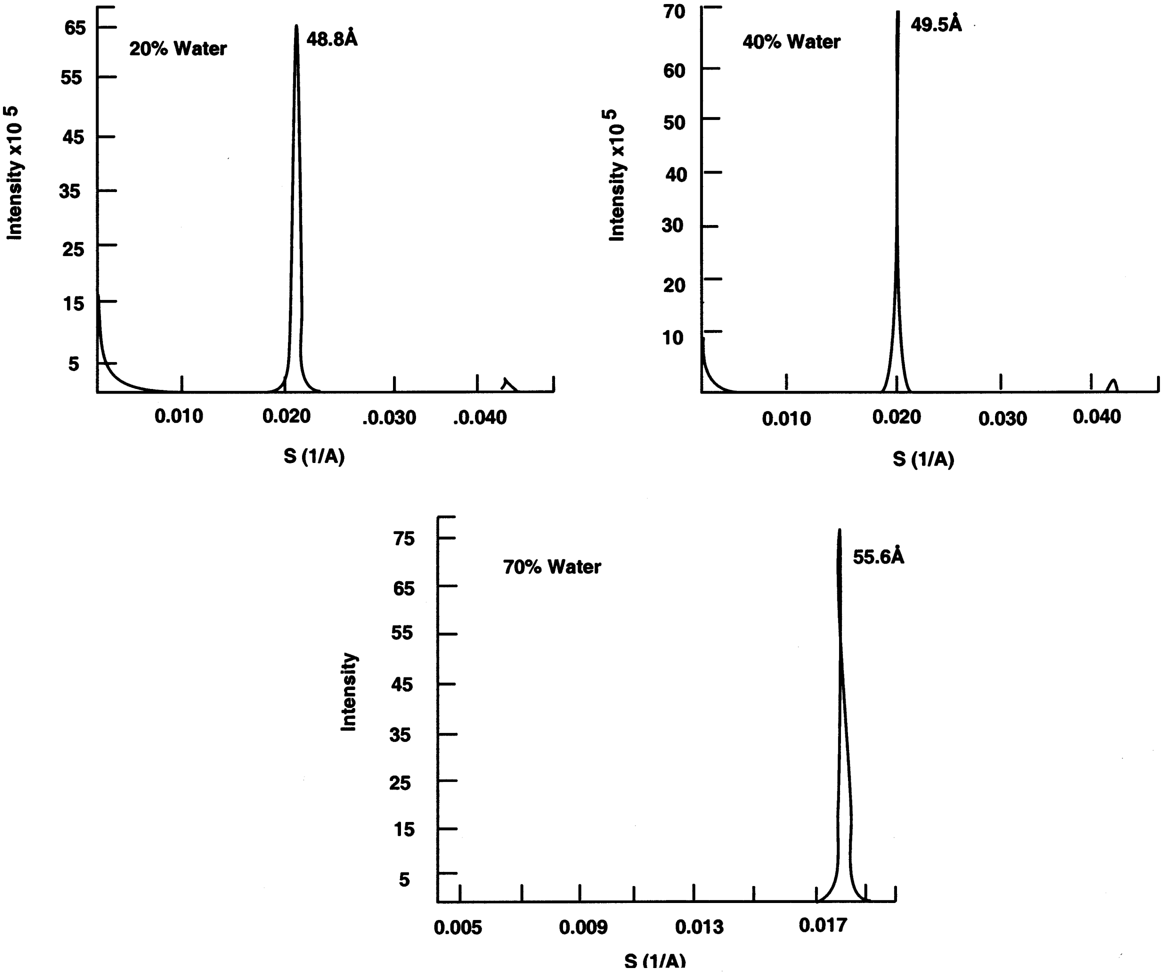

Fig. 4. Small angle X-ray diffraction data (synchrotron radiation source) of cetostearyl alcohol in controlled amounts of water.

w/w water) and its corresponding oil-in-water cream, both aged for 3 weeks. The spacings in the ternary system were over 500 Å and similar spacings were seen in the emulsion, confirming that significant swollen lamellar phase was present in the continuous phase of the cream. The changes in lamellar spacings with age for the model ternary gel and the corresponding cream are given in Table 1.

High angle data provided detailed information about the corresponding changes in short range order as this ionic ternary system swells (Table 2). At low water content (28% water) the high angle reflections are consistent with the presence of crystalline cetostearyl alcohol in monoclinic form. Diffraction spacings of 4.16 and 3.66 Å are consistent with those obtained for a cetostearyl alcohol mixture, described as sub-α phase by Stewart (1960). The d spacing observed at 2.87 Å almost indexes to the expected 110 spacing of a monoclinic sub-cell where $a = 3.66$ Å and $b = 4.16$ Å. Other weak reflections observed at 2.16 and 2.33 Å remain unassigned.

At water concentrations of 47% and above these bands were replaced by a single, very intense, broad reflection at 4.04 Å indicative of regular α-crystalline hexagonal packing of gel phase emulsifying wax bilayers. A weaker reflection at 3.57 Å indicated the presence of a small amount of excess crystalline cetostearyl alcohol remaining with the corresponding 100 reflection probably buried under the observed 4.06-Å band. The model ternary gel and the corresponding cream both showed an identical single reflection at 4.06 Å due to hexagonally packed emulsifying wax bilayers. In the cream, diffuse bands at 4.75 and 5.35 Å represented the presence of paraffin wax.

The influence of electrolyte (sodium chloride) on the swelling of the lamellar phase present in the model ternary gel and the cream is shown in Fig. 7 and the influence of changing the surfactant counterion from Br^- to Cl^- is shown in Fig. 8.

Fig. 9 compares the lamellar swelling for the model ternary system prepared with either pure or mixed homologue fatty alcohol and Table 3 shows the lamellar swelling of a cetrimide/pure alcohol system with age. High angle data for the pure cetyl alcohol system aged for 7 days are shown in Table 2. The pure alcohol ternary system gave the characteristic spacing at 4.06 Å, representing hexagonal lamellar phase. Strong reflections at ~4.15 and 3.61 Å are also present indicating that there were also cetyl alcohol crystals present in the monoclinic form.

4. Discussion

The results of this study confirm that the rheological properties of emulsions prepared with cetrimide/fatty alcohol mixed emulsifiers are con-

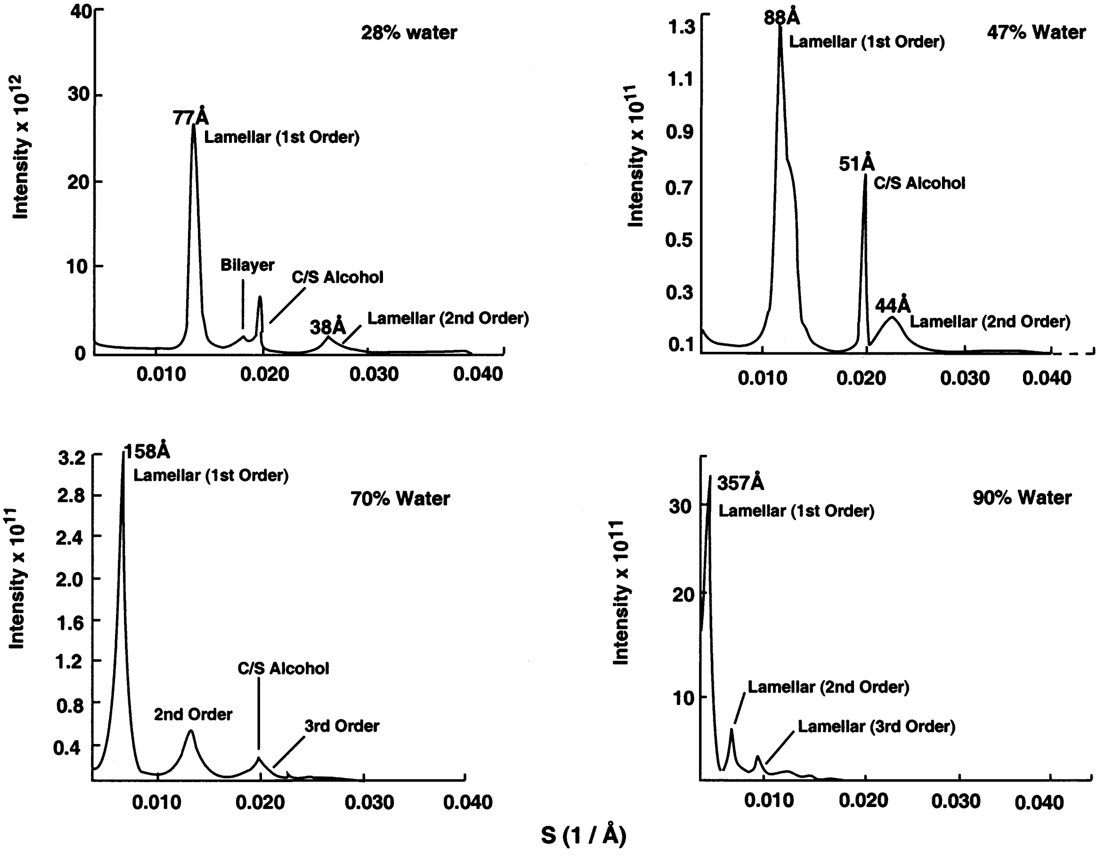

Fig. 5. Small angle X-ray diffraction data (synchrotron radiation source) of cetrimide/cetostearyl alcohol mixed emulsifier dispersed in 28, 47, 70 or 90% (w/w) water.

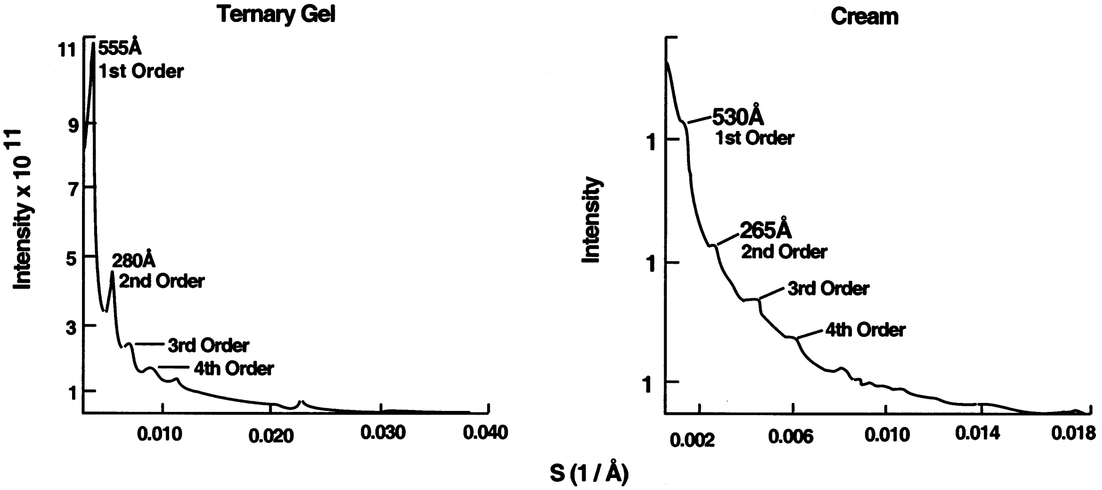

Fig. 6. Comparison of small angle X-ray diffraction (synchrotron radiation source) of cetrimide/cetostearyl alcohol ternary gel and the corresponding liquid paraffin-in-water cream. Both systems had been stored at 25°C for 3 weeks after preparation.

trolled by the stability and the swelling properties of a lamellar gel network phase. The heterogeneous nature of this phase make it difficult to obtain an accurate estimate of lamellar thickness, *d*, using microscopical techniques. However, this study has established that, despite the complexity of the systems, lamellar repeat distances can be measured accurately and unambiguously using synchrotron X-ray diffraction to give detailed information about water layer spacing. Comparison of the lamellar spacings with the rheological properties indicates that the thicker the interlamellar water layers, the higher the viscosity of the ternary gel or cream. This is because the volume ratio of the lamellar phase to the free continuous phase increases with the entrapment of water between emulsifying wax bilayers, giving higher apparent viscosities.

The structure of the networks is the subject of some controversy. Row and co-workers (Rowe, 1999) consider that the network consists of bilayers of cetostearyl alcohol containing interlamellar water, without incorporated surfactant. Our work, however, has demonstrated that the surfactant is an essential component of the gel network. The low angle X-ray data described in this paper confirms that the alcohol alone in excess water exhibits only limited swelling. Strong van der Waals forces of attraction between the polar head groups of the alcohol layers are balanced by osmotic repulsion. However, in the presence of small quantities of cetrimide (molar ratio of cetrimide/cetostearyl alcohol, 1:12), the alcohol exhibits a phenomenal swelling, similar to that reported with some charged lipids and amphiphiles (Krog and Borup, 1973; Hauser, 1984; Junginger, 1984) with the thickness of the interlamellar water, $d_{aq.}$, increasing continuously from 75 Å at 28% water to over 555 Å at ~93% water. The emulsifying wax bilayer distances, $d_{ew,}$ did not change significantly with added water so that at high water concentrations the thickness of interlamellar water layers (~500 Å) was over ten times that of the emulsifier bilayers (~50 Å). Comparison of low angle X-ray data for the

Table 1
Influence of storage time at 25°C on lamellar distance (Å)

Storage time	Lamellar distance (Å)	
	Ternary gel	Cream
1 day	476	–
3 days	525	460
3 weeks	555	530
6 weeks	625	–
6 months	664	570
3 years	810	–

Table 2
High angle diffraction (synchrotron radiation source) for cetrimide/fatty alcohol/water systems and a liquid-paraffin-in-water cream

Water (%w/w)	Diffraction spacing (Å)	Sub-cell
28	4.16, 3.66, 2.87, 2.33, 2.16	Monoclinic
47	4.04, 3.57	Hexagonal
90	4.06, 3.57	Hexagonal
Cetostearyl alcohol ternary gel	4.06	Hexagonal
Cetostearyl alcohol cream	4.05	Hexagonal
	4.75, 5.35	Paraffin wax
Cetyl alcohol ternary gel	4.06	Hexagonal
	4.15, 3.61	Monoclinic

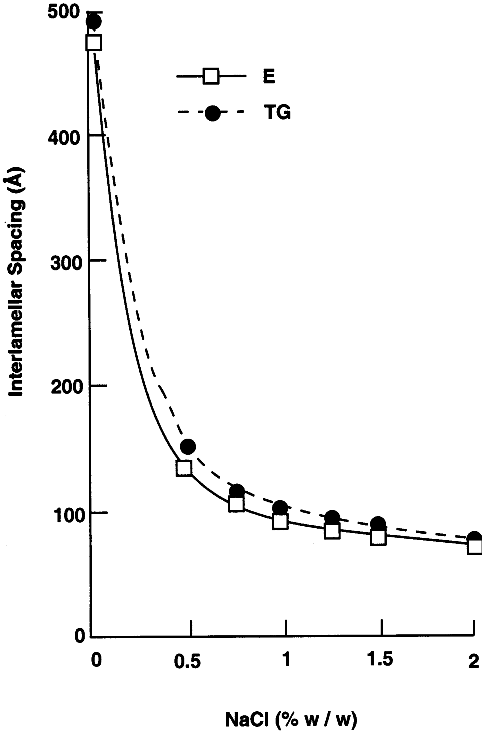

Fig. 7. Small angle X-ray diffraction data (synchrotron radiation source) to illustrate the influence of sodium chloride on the interlamellar spacings ($d_{aq.}$) of cetrimide/cetostearyl alcohol ternary gel and emulsion.

model ternary system and its corresponding emulsion confirms that the presence of paraffin oil does not alter the main structural characteristics of these complex systems and that the emulsion also contains extensively swollen bilayer structures. The photomicrographs suggest that the oil droplets act as a focus for multilayers of gel phase, which become more randomly oriented as they progress into the continuous phase. The emulsion is kinetically stable for long periods because the oil droplets are essentially immobilised in the rheologically stable structured continuous phase so that both flocculation and coalescence are inhibited.

The results from the high angle X-ray diffraction complemented the low angle work to give more information about the phase of the cetostearyl alcohol and also the mixed emulsifier head group spacings. The high angle data indicate that the crystalline cetostearyl alcohol alone and in ternary systems of low water content was in the predominantly monoclinic form. In this form the

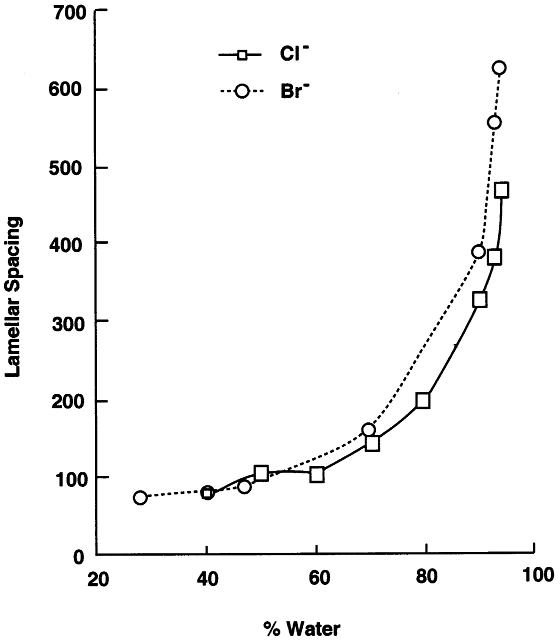

Fig. 8. Small angle X-ray diffraction data (synchrotron radiation source) of cetostearyl alcohol and either cetyltrimethylammonium bromide or cetyltrimethylammonium chloride in 93% water. Both systems had been stored at 25°C for 6 weeks after preparation.

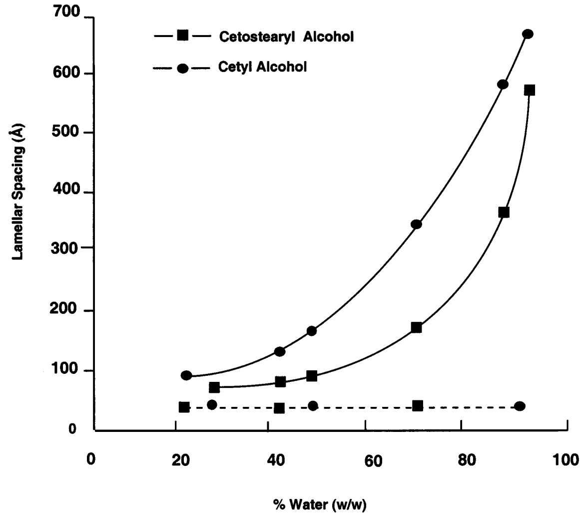

Fig. 9. Small angle X-ray diffraction data (synchrotron radiation source) to compare the bilayer swelling for the model ternary gel (93% water) prepared from either cetostearyl alcohol (after 3 weeks storage) or pure cetyl alcohol (after 6 days storage). The broken line represents the emulsifying wax bilayer distance (d_{ew}), which does not change with water content.

chains are non-rotating and are tilted towards the layer plane. At higher water concentrations, the swollen bilayers exhibited the α-crystalline mode of packing in which the hydrocarbon chains are packed in a hexagonal array and are oriented with their long axes at right angles to the layer planes and rotate about the axes (Tanaka et al., 1958).

The extensive swelling is electrostatic in nature. The surfactant molecules interpose themselves among the fatty alcohol molecules and electrical double layers arise from the dissociation and diffusion of counterions from the surfactant headgroups at the surface of the bilayers into the surrounding water. Electrostatic repulsion between adjacent bilayers arises from the overlap of the electrical double layers. The thickness of the double layers provides a measure of the range of electrostatic repulsion on which the water layer spacings depend. According to the DLVO theory, the double layer thickness $1/k$ is:

$$\frac{1}{k}=\left(\frac{\varepsilon_{\mathrm{r}}\varepsilon_0 RT}{4\pi F^2 \sum_i c_i z_i^2}\right)^{1/2} \tag{3}$$

where c_i and z_i are the concentration and valency of ions in the aqueous layers between the bilayers. ε_{r} and ε_0 are the dielectric constants of the dispersion medium and a vacuum, F is the Faraday constant, R is the gas constant and T the absolute temperature.

From Eq. (3), it is seen that the thickness of the double layer is inversely proportional to the square root of the concentration of electrolyte in the surrounding water. In water of low electrolyte concentration, thick double layers form so that the double layer force decays only slowly with separation between the charged bilayers resulting in large water spacings. Added electrolyte reduces swelling between the bilayers by a non-specific compression of the double layers. Thus in our systems, the addition of salt gave a significant reduction in lamellar swelling, until at ∼2.5% w/w salt the swelling was inhibited altogether. The viscosities reduced because the phase volume of the swollen lamellar structures decreased as excess water separated from the system. Examination of the separated upper layer containing 2% salt showed this to contain some plate-like monoclinic crystals.

Table 3
Small angle X-ray diffraction (synchrotron radiation source) of cetrimide/pure cetyl alcohol systems dispersed in controlled percentages of water after 6 and 18 days storage

	Lamellar distance (Å)				
Water (% w/w)	0	20	40	70	93
System age					
6 days	–	95.2	131.6	344	666
18 days	50	108	204	400	No diffraction peaks

Further evidence that the swelling behaviour is dependent on electrostatic repulsive forces is shown by the comparison between data for systems containing either chloride or bromide counterions. Both emulsifying waxes show the characteristic infinite swelling of the ionic ternary system in excess water. However, although at low water content the interlamellar spacings are similar, as the water content increases to above 70%, the extent of swelling is lower with the chloride counterion. Although the influence of charge on colloid stability is generally considered to be essentially independent of the nature of the counterion, the surface charge density needed to overcome the van der Waals forces of attraction between charged surfaces is extremely small in these extensively swollen systems. It is possible that the more electronegative Cl^- ion will decrease the repulsive forces between opposite lamellae by its effect on the surface charge density.

Our data for 90% water (*d* spacing of 357 Å) is similar to the *d* spacing of 340 Å found by Barry and Rowe (1989) using a Compact Kratky camera. However, it must be emphasised that they used a considerably lower cetrimide/fatty alcohol weight ratio (1:20) than that used in this work (1:9), and much greater swelling distances would be expected to occur in their systems. The current work has shown that the lamellar swelling proceeds far beyond the range that can be followed with reasonable accuracy by such conventional methods. Furthermore, measurements have been extended using synchrotron radiation to include model ternary gels containing over 93% water. These clearly show additional swellings, ranging from *d* spacings of 555 to 810 Å, depending on storage time (cf. Fig. 6, Table 1) with several orders of this lamellar spacing unambiguously visible. Similar lamellar spacings were visible in the corresponding cream. This increased lamellar phase swelling with age correlates with the observed rheology, for although cetostearyl alcohol creams and ternary gels are stable and semisolid for years, they do become less glossy and slightly thicker on storage (Barry and Saunders, 1970a). The low angle X-ray diffraction measurements indicate that the increases in consistency are due to the increases in lamellar distances which result in an increase in phase volume as more water is trapped between the emulsifying wax bilayers. This, in turn, suggests that on storage there is a rearrangement of the surfactant molecules in the bilayers leading to an effective reduction in the surfactant/alcohol ratio and hence counterion concentration.

The pure alcohol systems are rheologically unstable. Systems break down to become mobile as swollen α-crystalline networks crystallise into unswollen monoclinic crystals (Eccleston, 1976; Fukushima et al., 1977). The kinetics of breakdown shown here were unexpected, for there were initial increases in interlamellar distance as systems changed from semisolid to fluid, before the low angle diffraction peaks disappeared altogether. It is envisaged that, as the loosely packed swollen lamellar phase converts to the more closely packed monoclinic crystals, the surfactant with its relatively large headgroup would be gradually expelled from the emulsifying wax bilayers, temporarily reducing the effective surfactant/alcohol ratio and the counterion concentration causing increases in the interlamellar distances. The attractive forces holding the bilayers together, however, would get progressively weaker until the ultimate separation of swollen lamellar phase into monoclinic crystalline masses.

5. Conclusions

This study has confirmed that the rheological properties of aqueous creams containing cetrimide/fatty alcohol mixed emulsifier are controlled by the swelling properties of a lamellar gel network formed when the mixed emulsifier interacts with continuous phase water. X-ray diffraction experiments at the synchrotron radiation source have provided direct and accurate measurements of the interlamellar water spacings, despite the complexity of the systems studied. The cetrimide emulsifying wax was shown to exhibit a phenomenal electrostatic swelling in the continuous phase of the cream. The apparent viscosities of the creams decreased in the presence of increasing amounts of salt, and this was correlated with reductions in interlamellar swelling. Conversely, increases in consistency of the creams on storage were accompanied by increases in water layer thickness. Unstable systems, prepared with pure cetyl alcohol, showed initial increases in interlamellar water spacings, before the increasingly tenuous swollen lamellar phase collapsed into non-swollen crystals and water.

References

Abrahamsson, S., Larsson, G., von Sydow, E., 1960. The crystal structure of the monoclinic form of n-hexadecanol. Acta Cryst. 13, 770–774.

Barry, B.W., 1968. The self-bodying action of the mixed emulsifier sodium dodecyl sulfate/cetyl alcohol. J. Colloid Interface Sci. 28, 82–91.

Barry, B.W., 1974. Rheology of pharmaceutical and cosmetic semisolids. In: Bean, H.S., Beckett, A.H., Carless, J.E. (Eds.), Advances in Pharmaceutical Sciences. Academic Press, London, pp. 1–72.

Barry, B.W., Eccleston, G.M., 1973. Influence of gel networks in controlling consistency of o/w emulsions stabilised by mixed emulsifiers. J. Text. Stud. 4, 53–81.

Barry, B.W., Eccleston, G.M., 1973. Oscillatory testing of o/w emulsions containing mixed emulsifiers of the surfactant-long chain alcohol type: self-bodying action. J. Pharm. Pharmacol. 25, 244–253.

Barry, B.W., Eccleston, G.M., 1973. Oscillatory testing of o/w emulsions containing mixed emulsifiers of the surfactant/long chain alcohol type: influence of surfactant chain length. J. Pharm. Pharmacol. 25, 394–400.

Barry, M.D., Rowe, R.C., 1989. The characterisation by small-angle X-ray scattering of a pharmaceutical gel with a lamellar structure. Int. J. Pharm. 53, 139–143.

Barry, B.W., Saunders, G.M., 1970. The self-bodying action of the mixed emulsifier cetrimide cetostearyl alcohol. J. Colloid Interface Sci. 34, 300–315.

Barry, B.W., Saunders, G.M., 1970. Rheology of systems containing cetrimide/cetostearyl alcohol: variation with temperature. J. Pharm. Pharmacol. 22, 139–146.

Eccleston, G.M., 1974. The structure of the continuous phase in creams stabilised by cetrimide and cetostearyl alcohol. J. Pharm. Pharmacol. 27, 73P.

Eccleston, G.M., 1976. The structure and rheology of pharmaceutical and cosmetic creams. J. Colloid Interface Sci. 57, 66–74.

Eccleston, G.M., 1985. Phase transition in ternary systems and oil-in-water emulsions containing cetrimide and fatty alcohols. Int. J. Pharm. 27, 311–323.

Eccleston, G.M., 1986. The microstructure of semisolid creams. Pharm. Int. 7, 63–70.

Eccleston, G.M., 1990. Multiple-phase oil-in-water emulsions. J. Soc. Cosmet. Chem. 41, 1–22.

Eccleston, G.M., 1997. Functions of mixed emulsifiers and emulsifying waxes in dermatological lotions and creams. Colloids Surfaces, 169–182.

Fukushima, S., Yamaguchi, M., Harusawa, F., 1977. The effect of cetostearyl alcohol on the stabilisation of o/w emulsions. J. Colloid Interface Sci. 59, 159–165.

Goggin, P., Renren, H.E., Craig, D.Q.M., Gregory, D.P., 1997. An investigation into the use of low-frequency dielectric spectroscopy as a means of characterising the structure of creams based on aqueous cream BP. J. Pharm. Sci. 87, 559–564.

Griffiths, L., Horton, R., Parker, I., Rowe, R., 1992. NMR pulsed field gradient characterisation of the behaviour of water in gels and emulsions containing alcohol and cetrimide. J. Colloid Interface Sci. 154, 238.

Hauser, H., 1984. Some aspects of the phase behaviour of charged lipids. Biochem. Biophys. Acta 37–50.

Hill, R.M., Beckford, E.S., Rowe, R.C., Jones, C.B., Dissado, L.A., 1990. The characterisation of oil-in-water emulsions by means of a dielectric technique. J. Colloid Interface Sci. 138, 521–533.

Junginger, H.E., 1984. Colloidal structures of o/w creams. Pharm. Weekbl. 6, 141–149.

Krog, N., Borup, A.P., 1973. Swelling behaviour of lamellar phases of saturated monoglycerides in aqueous systems. J. Sci. Food Agric. 24, 691–701.

Patel, H.K., Rowe, R.C., McMahon, J., Stewart, R.F., 1985. A systematic microscopical examination of gels and emulsions containing cetrimide and cetostearyl alcohol. Int. J. Pharm. 25, 13–25.

Rowe, R.C., 1999. Molecules and microscopy, crystals and chromatgraphy-pharmaceutics in action. Pharm. J. 263, 430–435.

Rowe, R., McMahon, J., 1987. The characterisation of the microstructure of gels and emulsions containing alcohol and cetrimide using electron microscopy — a comparison of techniques. J. Colloid Interface Sci. 27, 367–373.

Rowe, R.C., Patel, H.K., 1985. The effect of temperature on the conductivity of gels and emulsions prepared from cetrimide and cetostearyl alcohol. J. Pharm. Pharmacol. 37, 564–567.

Stewart, F.H.C., 1960. Phase relationships and spreading behaviour of cetyl alcohol mixtures. Aust. J. Appl. Sci. 11, 157–168.

Tamburic, S., Craig, D.Q.M., Vuleta, G., Milic, J., 1996. A comparison of electrical and rheological techniques for the characterisation of creams. Int. J. Pharm. 137, 243–248.

Tanaka, K., Seto, T., Hayashida, T., 1958. Phase transformation of n-higher alcohols. Bull. Inst. Chem. Res. 35, 123–139.