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Short Communication

Properties of cetrimide/cetostearyl alcohol ternary gels; preparation effects

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Summary

A study has been made of the structure and properties of a ternary gel containing 0.5% w/w cetrimide and 4% w/w cetostearyl alcohol prepared using either a crash cooling technique as described by Barry and Saunders (1970) or a prolonged heating technique as described by Patel et al. (1985). Although the gel prepared by the latter method showed a more ordered structure with the liquid crystalline phase largely localized around the particles of cetostearyl alcohol and was more opaque, it was less conductive and less viscous than that prepared by the former method. Both gels contained 32–38% free water, the analysis of which revealed the presence of high concentrations of cetrimide. Speculations have been made concerning the differences in characteristics of the two gels.

The structure of gels and emulsions containing the mixed emulsifier system of cetrimide and cetostearyl alcohol has been extensively studied (Barry and Saunders, 1970; Barry, 1971) as recently reviewed by Eccleston (1984). However, a more recent study by Patel et al. (1985) has shown the structure of such systems to be more ordered than was previously suggested. The authors suggested that the difference may be due, at least in part, to the specific conditions used to prepare their systems. Since their conditions were chosen to provide an analogue of a large scale manufacturing process and hence were no more extraordinary than those used by previous

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workers, it would seem pertinent to study the effect of the two methods of preparation on the properties of these systems.

All the materials used in this study were of Pharmacopoeial grade. Two gels each containing 0.5% cetrimide and 4% cetostearyl alcohol were prepared by two methods. In the first procedure (Method 1) cetostearyl alcohol at 80°C was dispersed in aqueous cetrimide solution at the same temperature and stirred gently with a paddle stirrer for a period of 1 h before being allowed to cool to approximately 60°C. The dispersion was then homogenized using a Silverson multipurpose high-speed mixer for a period of 15 min or until the setting point of the gel was reached. The gel was then allowed to cool to room temperature. In the second procedure (Method 2) the two phases were mixed at 70°C and then immediately homogenized for 2 min before being cooled rapidly to room temperature while still being stirred. Both gels were allowed to stand for 2 weeks before being tested.

The opacity and light scattering of the gels were quantified using reflectance measurements (Rowe and Patel, 1985a) and visual assessment was carried out using differential interference contrast microscopy and freeze-etch electron microscopy (Patel et al., 1985). The conductivities of the gels were determined at 25°C using a simple conductivity cell in the form of probe coupled to a Universal Autobalance Bridge (Wayne Kerr, Type B642). Rheological data was generated using a Deer rheometer (Sangamo Schlumberger) fitted with a single concentric cylinder arrangement. The gels were analyzed by both creep and continuous shear rheology and the "true" yield point, viscosity and shear modulus determined.

The amount of free water (as opposed to that bound up in the lyotropic liquid crystalline phase) expressed as a percentage of the total weight was evaluated using both thermogravimetric analysis and ultracentrifugation. The thermogravimetric technique was similar to that used by Junginger et al. (1984). A sample (6–8 mg) of each gel was placed on the scale pan of a thermogravimetric analyzer (Perkin-Elmer, Model TGS-2) and heated at a rate of $2°C \cdot min^{-1}$ from 20 to 100°C. The weight loss graph was analyzed as suggested by Junginger et al. (1984). In addition 4–5 g of

Table 1
THE EFFECT OF THE METHOD OF PREPARATION ON THE PROPERTIES OF A GEL PREPARED USING THE MIXED EMULSIFIER SYSTEM OF CETRIMIDE AND CETOSTEARYL ALCOHOL

Property	Method 1	Method 2
Specific conductivity (μmho.cm^{-1})	33.38	47.08
Scattering index (mm^{-1})	0.1591 ± 0.017	0.1381 ± 0.017
Reflectivity (%)	25.9	21.5
True yield (Nm^{-2})	3.0	8.0
Shear modulus (Nm^{-2})	8.0	36.0
Viscosity @ 100 s^{-1} (mPas)	129	188
Free water (% w/w)		
Determined by T.G.A.	33.7	32.0
Determined by ultracentrifugation	37.4	38.0

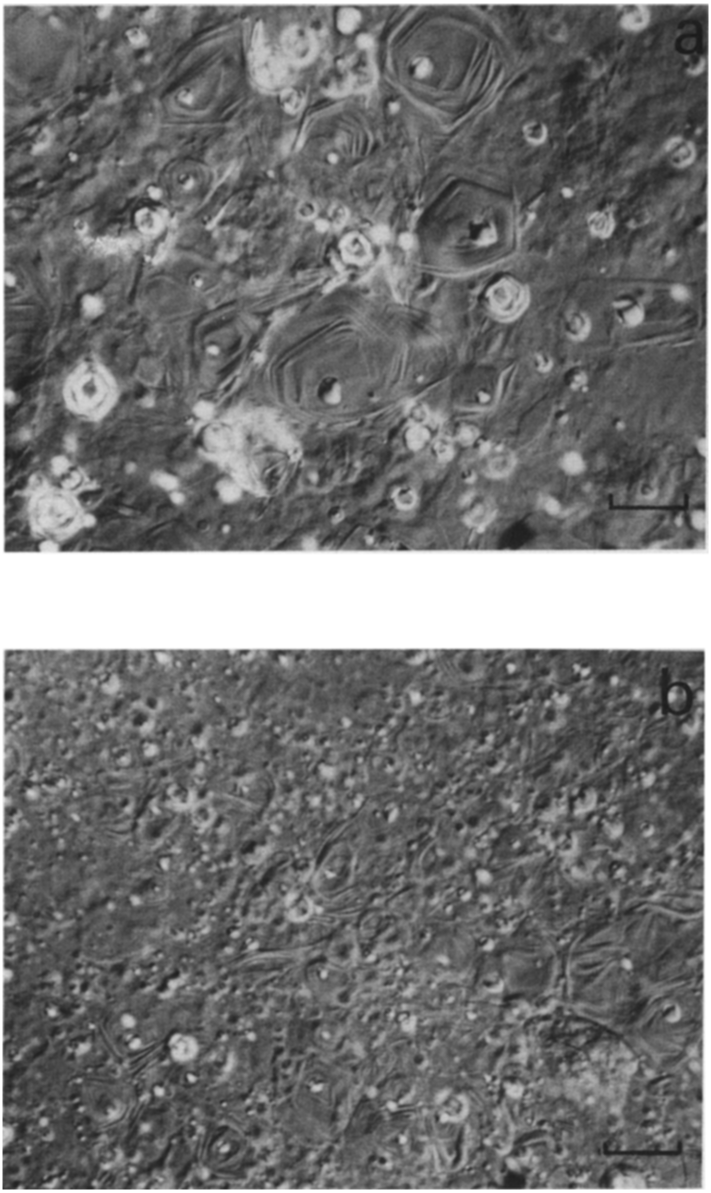

Fig. 1. Photomicrographs of a ternary gel prepared using 0.5% w/w cetrimide and 4.0% w/w cetostearyl alcohol. (a) By Method 1 and (b) by Method 2. (1 division = 25 μm.)

each gel was centrifuged at 15×10^4 *g* for 3 h using an ultracentrifuge (Beckman, Model L5-65B) and the amount of free water (the bottom layer) determined by weighing. Analysis of the water for free cetrimide was determined by conductivity measurement.

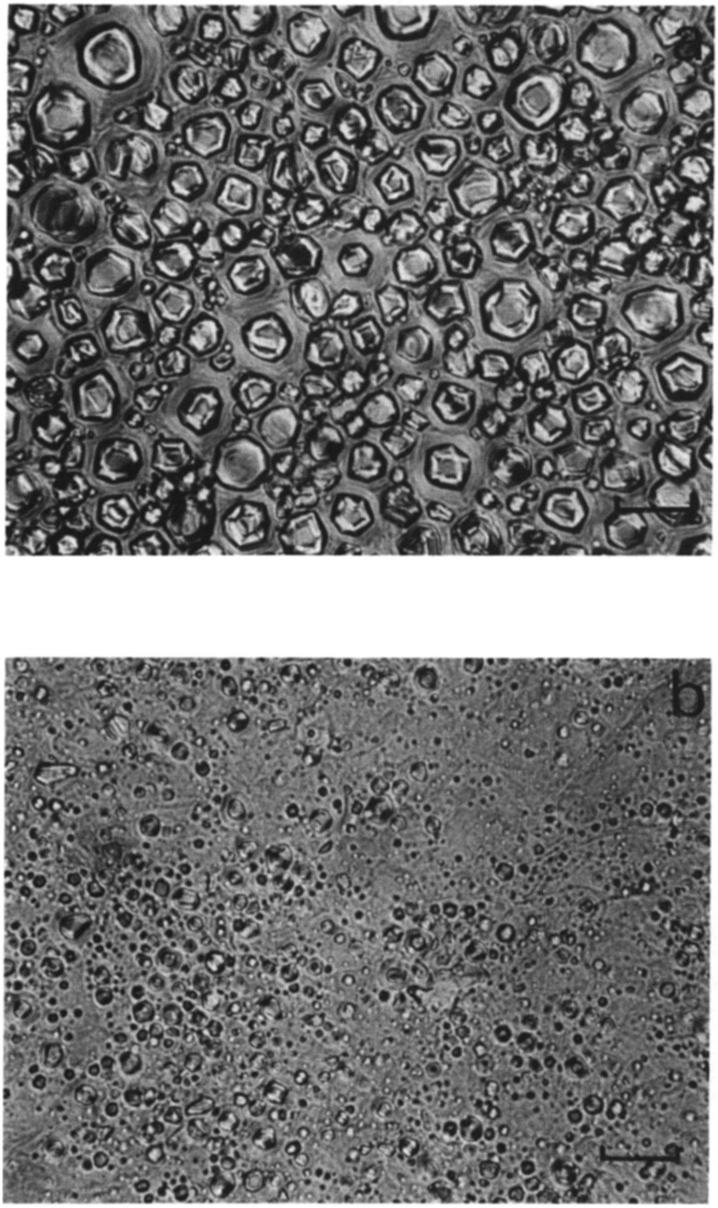

Fig. 2. Photomicrographs of a concentrated sample (the top layer) of a gel prepared by (a) Method 1 and (b) Method 2 obtained by ultracentrifugation at 15×10^4 *g*. (1 division = 25 μm.)

The results generated for each gel are shown in Table 1 and Figs. 1 and 2. From the differential interference contrast photomicrographs (Fig. 1) it can be seen that the gel prepared by Method 1 exhibits a more ordered structure with the lyotropic liquid crystalline network enveloping the relatively large (~ 15 μm) cetostearyl alcohol particles. On the other hand, the gel prepared by Method 2 exhibits a more random structure with the lyotropic liquid crystalline phase more extended and only some localized around particles of cetostearyl alcohol that are smaller (~ 5 μm) but greater in number. The differences in size of cetostearyl alcohol particles is more clearly illustrated by microscopical examination (Fig. 2) of a concentrated sample of gel (the top layer) obtained by ultracentrifugation. In addition, the gel prepared by Method 1 exhibits a greater uniformity in size of particles than those of the gel prepared by Method 2. The freeze-etch electron micrographs confirmed the interpretation of the optical micrographs.

The conductimetric and rheological data are consistent with the microscopical data. In the more ordered gel prepared by Method 1 the free water will be in the interstices formed between the cetostearyl alcohol particles with their swollen envelope of liquid crystal and hence the conductive pathway will be effectively increased due to the increased tortuosity. The more random structure in the gel prepared by Method 2 will, on the other hand, allow a greater freedom of movement of ions leading to a higher conductivity. The reason for the increased viscosity in the gel prepared by Method 2 can be considered to be analogous to the increased viscosity that occurs when a polymer is dissolved in a good solvent as opposed to a poor solvent, i.e. extended chains always produce a higher viscosity than those that are tightly coiled (Rowe and Patel, 1985b). However, this may not be the full story since it is well known in particulate dispersions involving interacting particles, that the size and number of the dispersed phase can have a significant effect on viscosity with systems containing a large number of smaller particles having a higher viscosity than those of a similar phase volume but fewer and larger particles (Stewart and Sutton, 1984).

The fact that there was no difference in the amount of free water present in both gels would suggest that the rate of formation of the lyotropic liquid crystalline phase is extremely fast. Analysis of the free water for cetrimide revealed that in both cases there was still in excess of 0.35% w/w unreacted cetrimide. This would imply that the accepted pictorial representation of the lyotropic crystalline phase as being an equimolar distribution of cetrimide and cetostearyl alcohol is incorrect—a ratio of one molecule of cetrimide to at least 20 molecules of cetostearyl alcohol would appear to be more acceptable. This has recently been confirmed by Laser Raman Spectroscopy (Louden et al., 1985). It may even be possible that the cetrimide primarily acts to lower the interfacial tension between the molten cetostearyl alcohol droplets and the water allowing a favourable environment for water to associate with the alcohol to form the liquid crystalline phase. This is not as extraordinary as it would appear at first sight. It is well known in food science that food emulsifiers of similar HLB to cetostearyl alcohol can form lamellar liquid crystalline phases in water when the systems are heated above their mesophase formation temperatures (Krog, 1976). Free cetrimide is also necessary for the antiseptic properties of such systems.

In conclusion, it can be seen that the method of preparation can affect the properties of gels prepared using the mixed emulsifier system of cetrimide and cetostearyl alcohol, and that, by studying this effect using a variety of techniques hitherto not used for this specific system, it has been possible to gain further insight into the structure of this system.

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