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COMMUNICATIONS

Water distribution in creams prepared using cetostearyl alcohol and cetrimide

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The water distribution in an antiseptic cream formulation prepared using cetostearyl alcohol and cetrimide has been studied using thermogravimetric analysis, differential scanning calorimetry, ultracentrifugation and scanning electron microscopy. In addition to a free water phase two types of interlamellarly fixed water were found, one associated with the liquid crystalline network around the oil droplets and one associated with the liquid crystalline network of the bulk. The latter was in equilibrium with the free water and can be classed as freely drainable.

The mixed emulsifier system of cetrimide and cetostearyl alcohol is often used in the preparation of antiseptic creams. The structure of these creams is very complex consisting of droplets of liquid paraffin together with particles of excess cetostearyl alcohol dispersed in a liquid crystalline network consisting of bilayers of cetostearyl alcohol (lamellae) swollen with water (Patel et al 1985a). Recent work on similar emulsion systems using thermogravimetric analysis (Junginger et al 1984) has shown that it is possible to differentiate quantitatively between the free water and the water between the bilayers—the so called interlamellarly fixed water. This technique along with ultracentrifugation, differential scanning calorimetry and scanning electron microscopy has been used to investigate water distribution in an antiseptic cream formulation prepared using cetostearyl alcohol and cetrimide.

Materials and methods

All the materials were of pharmacopoeial grade. A cream containing 0·5% w/w cetrimide, 10% w/w cetostearyl alcohol, 10% w/w liquid paraffin with 0·02% w/w hydroxybenzoates as preservative was prepared by the prolonged healing method described by Patel et al (1985b). This involved heating both the lipophilic (liquid paraffin and cetostearyl alcohol) and aqueous phases (cetrimide solution and hydroxybenzoates) to 80 °C, mixing them followed by gentle stirring with a paddle stirrer for 1 h before cooling to 60 °C. The dispersion was then homogenized using a Silverson multi-purpose high speed mixer until the setting point of the cream was reached. The cream was then allowed to cool to room temperature (20 °C).

Water distribution within the cream was assessed by three methods; thermogravimetric analysis (Model TG50, Mettler Instrumente A.G., Switzerland), ultracentrifugation (Model L5–65B, Beckman RIIC Ltd, UK) and differential scanning calorimetry (Model DSC 30, Mettler Instrumente A.G., Switzerland). In thermogravimetric analysis a small sample (≈5 mg) evenly spread on a piece of aluminium foil was placed on the scale pan of the thermogravimetric analyser and heated at a rate of 2 °C min^{-1} from 4 to 70 °C. The weight loss graph was analysed as suggested by Junginger et al (1984). In ultracentrifugation, samples (≈5 g) were centrifuged at $15 \times 10^4 g$ for 18 h and the amount of free water (the bottom layer) determined by weighing. In differential scanning calorimetry, samples (≈5 mg) were crash frozen to −30 °C in liquid nitrogen. After equilibration the samples were then heated at 2 °C min^{-1} and the endotherm at 0 °C (indicating the melting of water) analysed to determine the total (freezable) water content of the cream. Between 4 and 6 samples were tested using each technique and the means and standard deviations calculated.

The structure of the cream was examined using cryogenic scanning electron microscopy. This involved crash freezing the sample in slushy liquid nitrogen, fracturing the frozen sample, etching it at −80 °C and 10^{-2} torr and finally coating it with gold. Unlike the more commonly used technique of freeze etch transmission electron microscopy where a replica of the fracture surface is examined (Patel et al 1985a) this technique enabled a direct examination of the fractured surface (Rowe & McMahon unpublished observation).

Results and discussion

An examination of the thermogravimetric data, of which Fig. 1 is representative, showed that there were

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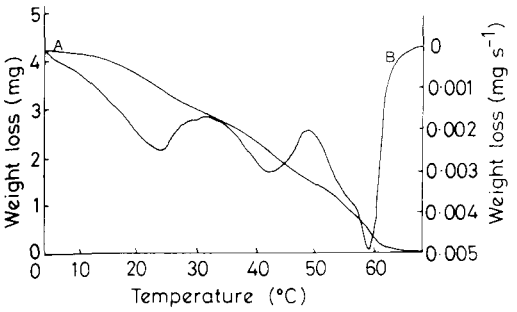

FIG. 1. A representative thermogravimetry curve (A) integral and (B) differential showing the three steps in weight loss.

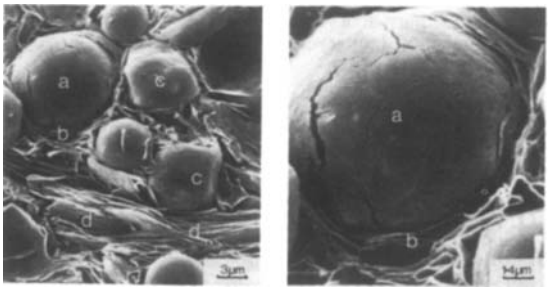

FIG. 2. Scanning electron micrographs of a freeze-fractured and etched surface of the cream: a is an oil droplet acting as a nucleus for the liquid crystalline network, b; d is the liquid crystalline network of the bulk; c is an irregularly shaped cetostearyl alcohol particle.

three distinct inflections in the weight loss curve; the first peaking at 23–25 °C and ending at 30–33 °C, the second peaking at 41–43 °C and ending at 48–49 °C and the third peaking at 53–59 °C ending at 62–67 °C with weight losses of 24·4 ± 1·1%, 27·0 ± 3·2% and 25·5 ± 3·5%, respectively. Although the total weight loss of 76·6% was slightly low compared with the theoretical value, it compared favourably with the total freezable water content of 76·5% ± 0·3% determined by differential scanning calorimetry. This discrepancy may be due to either water loss during the manufacturing process or water present as hydrates of cetostearyl alcohol. The free water determined by ultracentrifugation amounted to 13·9 ± 0·3%.

The presence of three steps in the thermogravimetric data, as opposed to the two seen by Junginger et al (1984), needs more explanation. The first step ending at 30–33 °C is almost certainly due to free water. The discrepancy between the value recorded by thermogravimetry and the 13·9% recorded by ultracentrifugation is due to the deficiencies inherent in the latter method. Separation of water under centrifugation will be dependent on the viscosity of the sample which itself will be increasing as water is lost. Under these conditions with a sample with a very high initial viscosity it is unlikely that full separation will occur even at the prolonged times used here. The third step starting at 48–49 °C and ending at 62–67 °C can definitely be assigned to the melting of the liquid crystalline network since this has been observed at these temperatures using a variety of independent techniques, e.g. hot stage microscopy, conductivity and rheometry.

The origin of the second step is less clear. Pointers may be obtained, perhaps surprisingly, by an examination of the thermogravimetric data on the various layers in the centrifuged sample. Previous examination of centrifuged samples (Patel et al 1985b) has shown that the oil droplets and excess cetostearyl alcohol particles invariably form the top layer with a middle layer consisting of liquid crystalline network. Thermogravimetric analysis of the middle layer of the centrifuged cream yielded only two inflections corresponding to the first two for the initial sample, while that of the top layer yielded three inflections analogous to those for the initial sample. This information shows (i) that not all the free water has been separated, (ii) that the second step is associated with the liquid crystalline network and (iii) that the third step is associated with either the oil droplets or excess cetostearyl alcohol particles.

Scanning electron photomicrography of the cream (Fig. 2) certainly shows that there are indeed two distinct 'types' of liquid crystalline network, one associated with the oil droplets and the other more randomly orientated in the bulk. It is proposed that in the former the water is entrapped while in the latter the water is in equilibrium with the free water, i.e. it is freely drainable.

The results show that thermogravimetric analysis is a useful tool in understanding the structure of these complex systems. It is recommended that the analysis be started at below ambient temperature, preferably below 10 °C, since significant water loss does occur at such temperatures.

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