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A preliminary examination of the structure of gels and emulsions containing cetostearyl alcohol and cetrimide using Laser Raman Spectroscopy

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Summary

The structure of gels and emulsions containing the mixed emulsifier system of cetrimide and cetostearyl alcohol has been studied using both macro and micro Laser Raman Spectroscopy. It has been shown that, whereas the former provides information of the relative changes in overall structure in the system, the latter provides detailed information of the individual components. Evidence from these techniques suggests that the lyotropic liquid crystalline phase in both the emulsions and the gel systems consists primarily of cetostearyl alcohol. It has also been possible to identify cetostearyl alcohol in the droplets of liquid paraffin in the emulsion. The results indicate the potential of these rapid and non-destructive techniques in the microanalysis of such systems.

Introduction

The mixed emulsifier system of cetrimide and cetostearyl alcohol is frequently used in the formulation of antiseptic creams and much work has been done in an attempt to define the composition of the various phases within the cream using

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various microscopic techniques (Barry and Saunders, 1970; Eccleston, 1984; Patel et al., 1985a). However, as yet, there has been no attempt to independently identify and analyze the various phases in order to confirm the subjective opinions of the microscopists. A technique that has recently become available in this respect is Laser Raman Spectroscopy (Tobin, 1971; Long, 1977). The Raman effect is well known and occurs when polyatomic molecules (both inorganic and organic) are irradiated with a monochromatic light beam, the spectra so formed being a unique finger-print of the chemical species. More recently, due to the pioneering work of Delhaye and Dhamelincourt (1974, 1975) and Rosasco et al. (1974, 1975), Laser Raman Spectroscopy has been developed as a microanalytical tool and it is now possible, by means of a specialized microprobe, to obtain the Raman spectra of, and hence qualitatively identify, particles inside transparent media down to 1 μm in diameter without specialized preparative techniques. In this work we have used a specialised Raman microprobe (Cook and Louden, 1979) to study the structure of both gels and emulsions prepared using the mixed emulsifier system of cetrimide and cetostearyl alcohol together with liquid paraffin and water.

Materials and Methods

Preparation of the gels and emulsions

All the materials used were of Pharmacopoeial grade. The ternary systems T_1-T_8 were prepared according to the formulae in Table 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 mixture was then homogenized using a Silverson multipurpose high speed mixer until the setting point of the gel was reached or for a period of not more than 15 min. The gel was then allowed to cool to room temperature. The emulsion E_1 was prepared in a similar fashion except that the cetostearyl alcohol was dissolved in the liquid paraffin at 80°C before being added to the aqueous cetrimide solution at the same temperature. All systems were allowed to stand for at least 2 weeks before being tested.

Laser Raman Spectroscopy

The Raman microprobe used in this study consisted of a modified Nikon Optiphot optical microscope coupled to a Jobin Yvon HG25 double monochroma-

TABLE 1

FORMULATIONS USED IN THIS STUDY (ALL CONCENTRATIONS % w/w)

	T_1	T_2	T_3	T_4	T_5	T_6	T_7	T_8	E_1
Cetrimide	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Cetostearyl alcohol	0.25	0.5	1.0	2.5	4.0	6.0	8.0	10.0	10.0
Liquid paraffin	–	–	–	–	–	–	–	–	5.0
Purified water to:	100	100	100	100	100	100	100	100	100

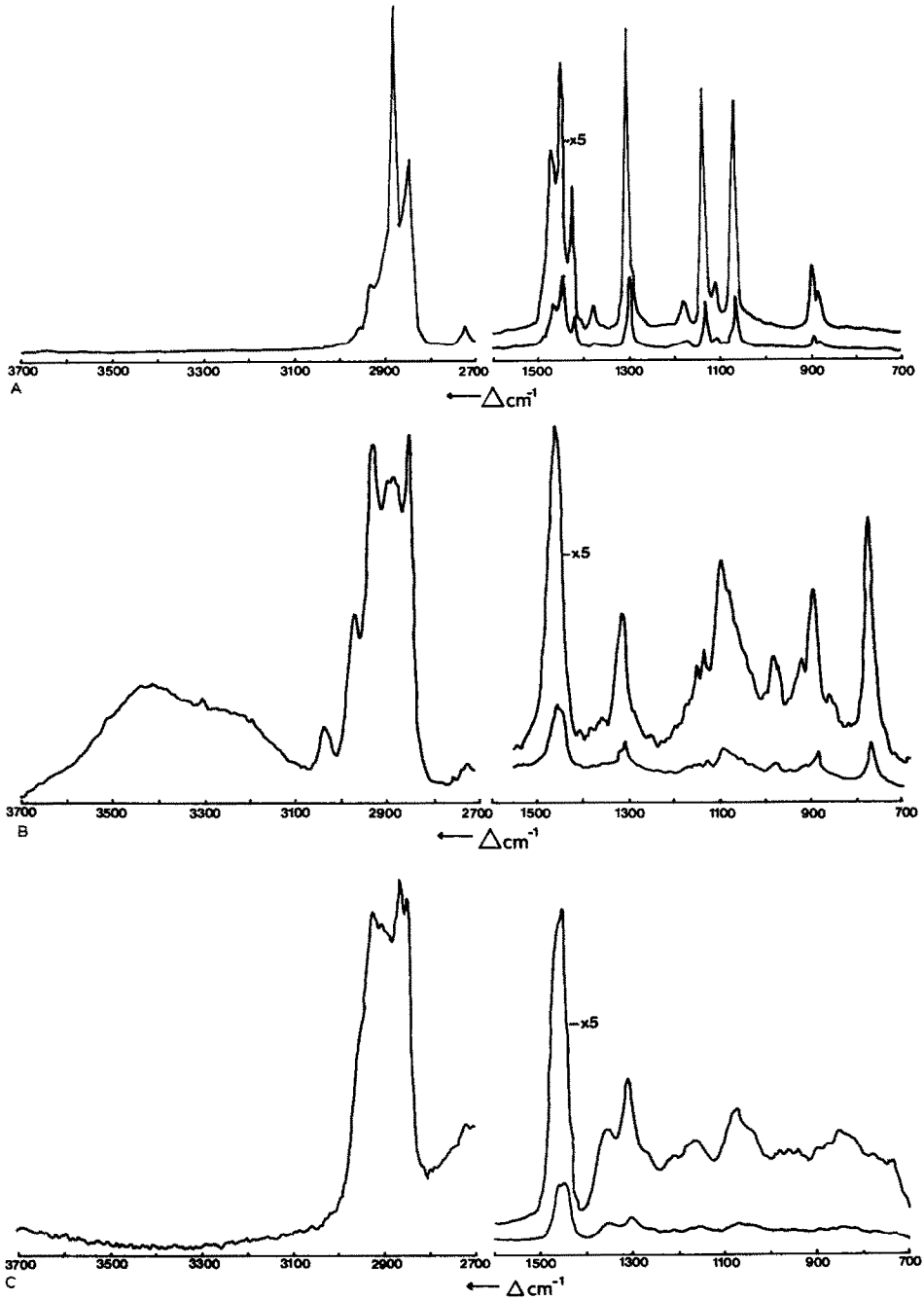


Fig. 1. Raman spectra of: (A) cetostearyl alcohol; (B) cetrimide 40% w/w solution; and (C) liquid paraffin used in this work.

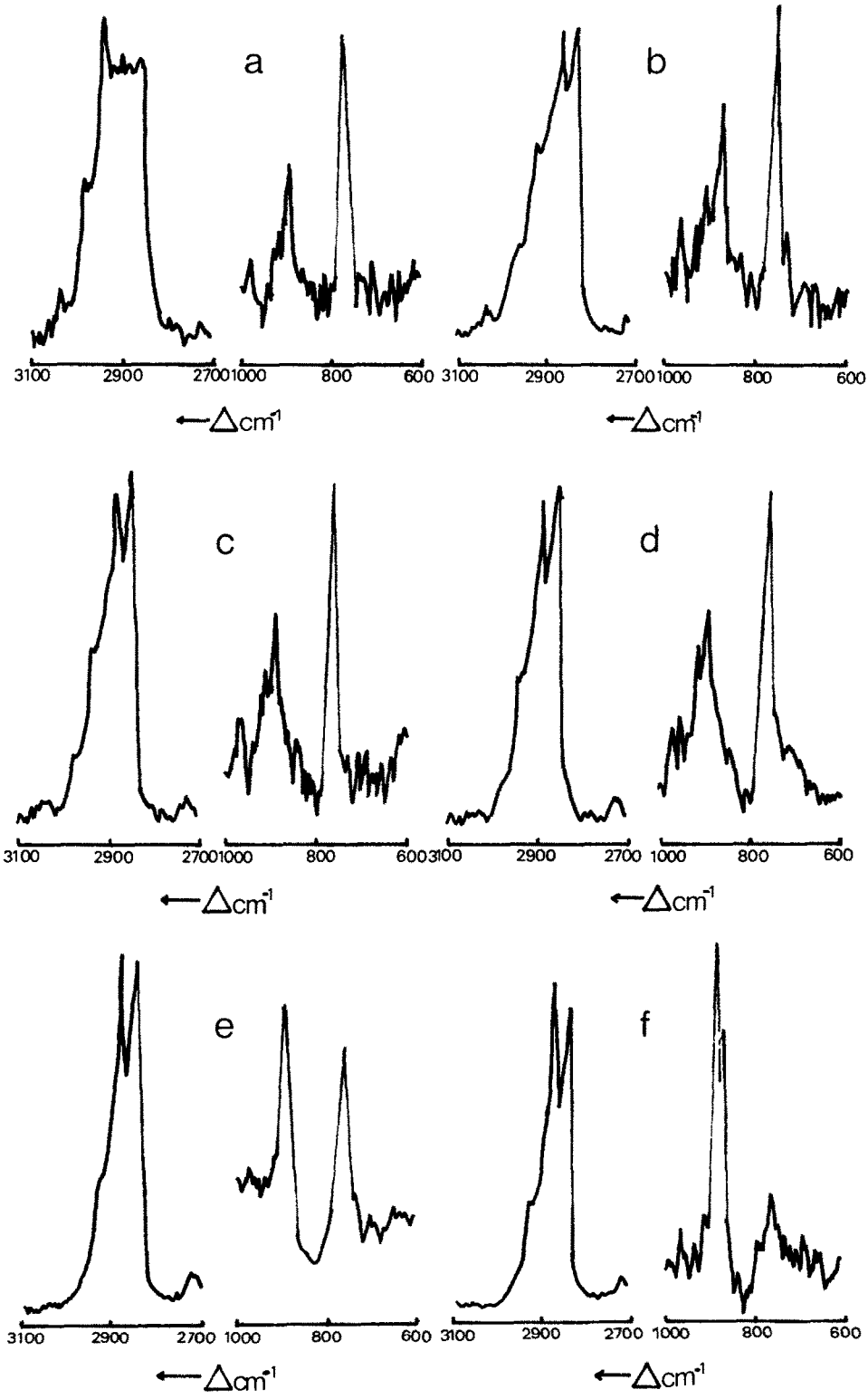
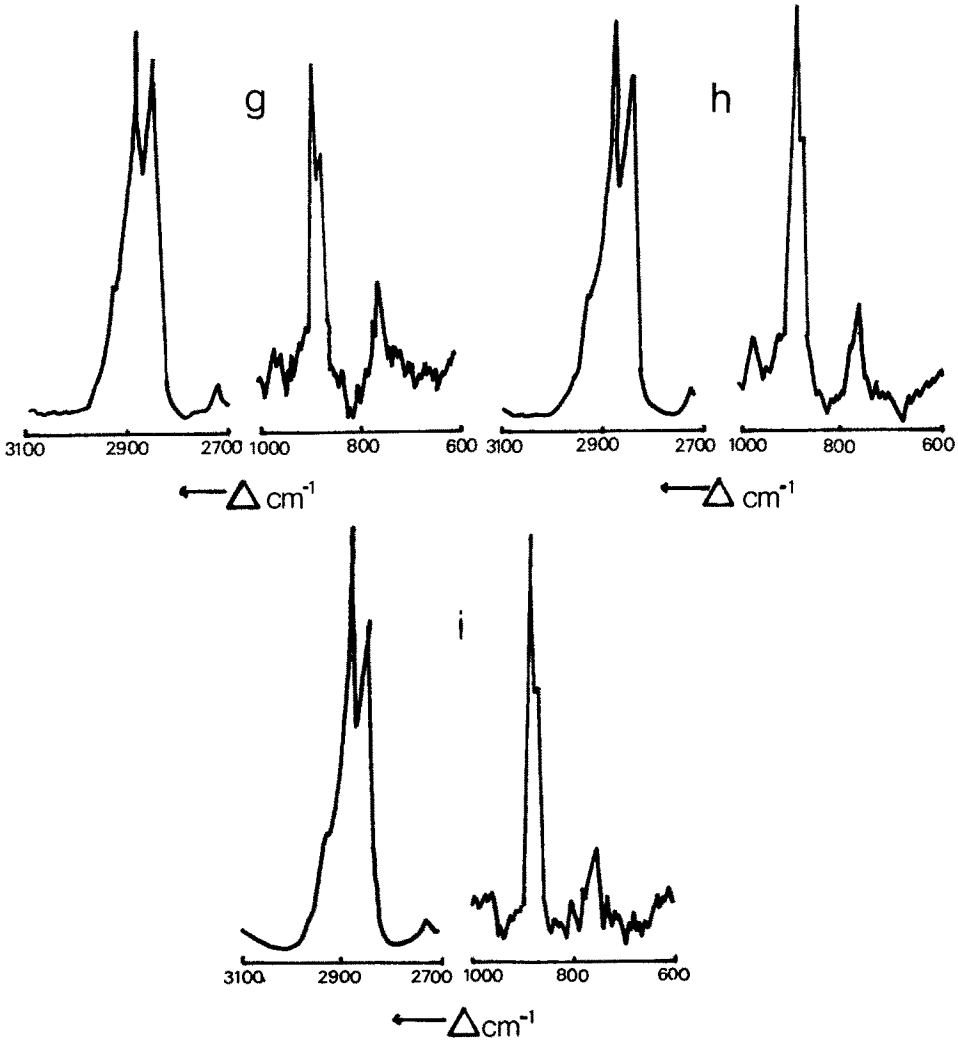


Fig. 2.



← Fig. 2. Raman spectra of the bulk ternary gels showing the effect of increasing the cetostearyl alcohol. (a) 0.5% w/w aqueous cetrimide; (b), (c), (d), (e), (f), (g), (h) and (i) are spectra of gels T_1–T_8, respectively.

TABLE 2

TYPICAL OPERATING CONDITIONS FOR LASER RAMAN SPECTROSCOPY

	'Macro' Raman Spectroscopy	'Micro' Raman Spectroscopy
Laser	500 mW at head 30 mW at sample	900 mW at head 40 mW at sample
Objective lens	40×0.55 NA	100×0.9 NA
Slit width	500 μm	500 μm
Scan rate	100 $cm^{-1} \cdot min^{-1}$	100 $cm^{-1} \cdot min^{-1}$
Time constant	1 s	1 s
Range	2700–3700 cm^{-1} and 600–1600 cm^{-1}	2700–3700 cm^{-1}

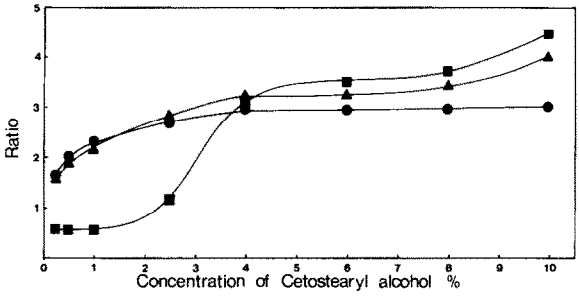


Fig. 3. Graphs of the relative intensities of the peaks at 770, 890, 2840, 2880 and 2925 cm^{-1} vs concentration of cetostearyl alcohol. ■, 890/770; ▲, 2880/2925; ●, 2840/2925.

tor. The detection system was a RCA C31034A gallium arsenide photomultiplier tube with an Ortec Brookdeal 5C1 photon counting system and an 1S1T (intensified silicon intensified target) optical multichannel detector system. Laser excitation was the 488 nm blue line of a Coherent Innova 90-2 Argon ion gas laser.

Samples for analysis were contained in two ways, the 'macro' Raman spectra of the bulk ternary gels was obtained by placing the gels in a thin walled capillary tube, the 'micro' Raman spectra of the same systems were obtained on samples in the form of a 20 μm thick film between a glass coverslip and microscope slide. Each

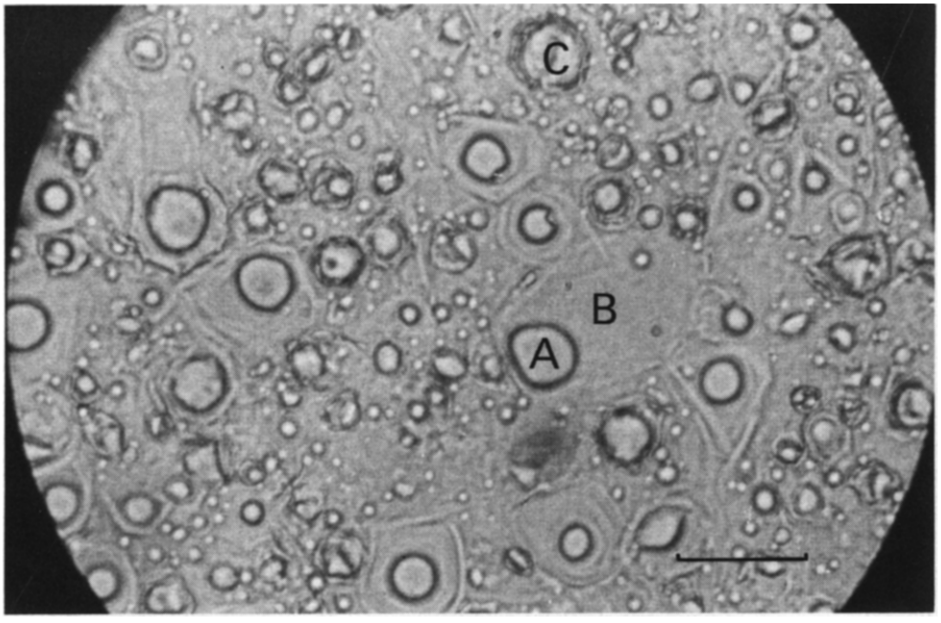


Fig. 4. Photomicrograph of the ternary gel T_8 containing 10% w/w cetostearyl alcohol. 1 division = 20 μm.

sample was first examined on the microscope using white light illumination and a viewing head or a close circuit television viewing system. The point/area of interest was located and positioned centrally in the field of view. The laser beam was focused to a diffraction-limited spot (minimum 1 μm in diameter) by the microscope objective lens and the back scattered radiation collected by the same objective lens and directed into the monochromator. The dispersed radiation was then detected by the photomultiplier tube or the multi-channel detector. All spectra were first recorded into a Nicolet 1070 instrument computer for data manipulation, i.e. averaging of spectra for weak signals (600–1000 cm^{-1} range) and background subtraction, and then plotted onto a chart recorder. Typical conditions for obtaining spectra were as given in Table 2.

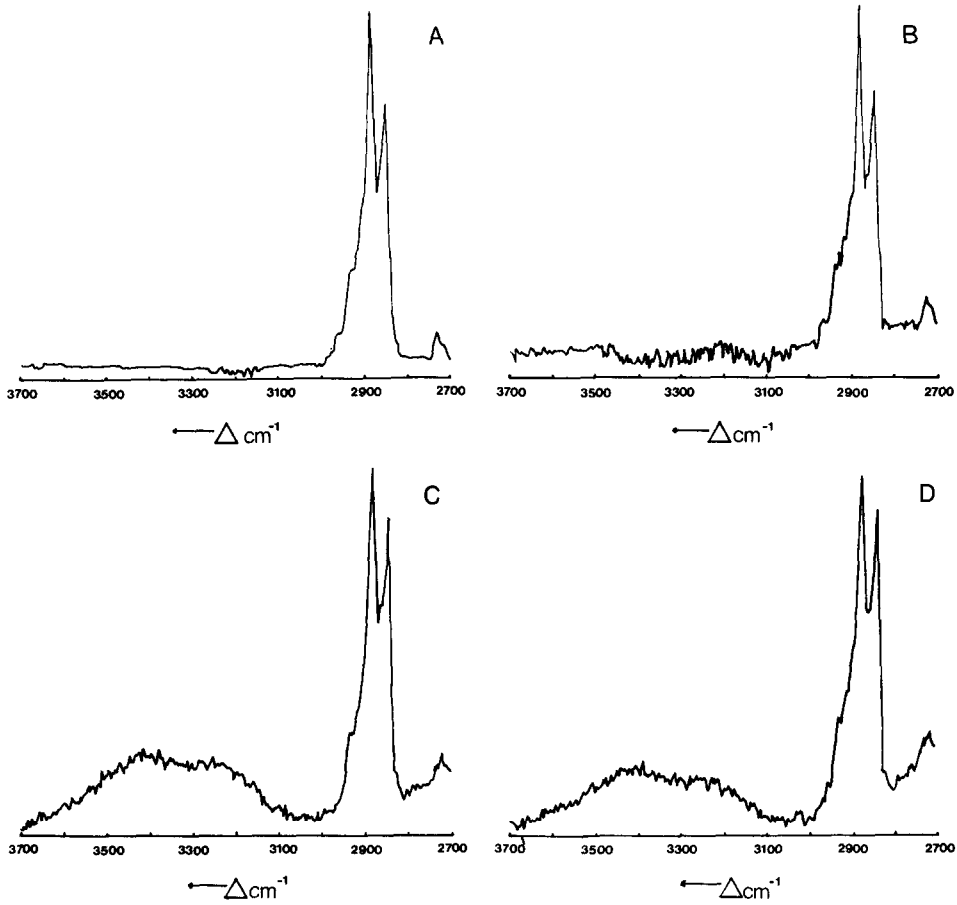


Fig. 5. Raman spectra of the features A, B, C and D annotated in Fig. 4.

Results and Discussion

Fig. 1 shows the spectra of the materials used to prepare the gels and emulsions. Cetrimide was used as a 40% w/w aqueous solution hence the broad band between 3100 and 3600 cm^{-1} due to the –OH stretching vibration of the water present. It is interesting to note that in the –C–H stretching vibration region between 2700 and 3100 cm^{-1} all three materials show peaks at 2840 and 2880 cm^{-1} but while in cetrimide the 2840 peak is predominant, the 2880 peak is predominant in the case of both the cetostearyl alcohol and liquid paraffin. In addition, both cetrimide and liquid paraffin show major peaks at 2925 cm^{-1} but in cetostearyl alcohol there is only a minor peak at this wave number. Within the 'finger-print' region below 1000 cm^{-1} cetrimide can be readily identified by peaks both at 770 cm^{-1} and 890 cm^{-1} the latter also being a minor peak in the cetostearyl alcohol spectrum. These differences in the spectra can be utilized to study the interaction of the cetostearyl alcohol and cetrimide in the formation of the ternary gels T_1–T_8. The spectra obtained on the bulk samples of these gels are shown in Fig. 2. It can be seen that the most significant changes in the spectra on increasing the cetostearyl alcohol concentration occur in the finger-point region of 600–1000 cm^{-1} where there is a large decrease in the height of the peak at 770 cm^{-1} accompanied by an increase in the height of the peak at 890 cm^{-1}. However, a graph of the ratio of these peak heights when plotted against cetostearyl alcohol concentration (Fig. 3) is not linear but sigmoidal in shape with inflections at approximately 1.5–2.0% w/w and 4%

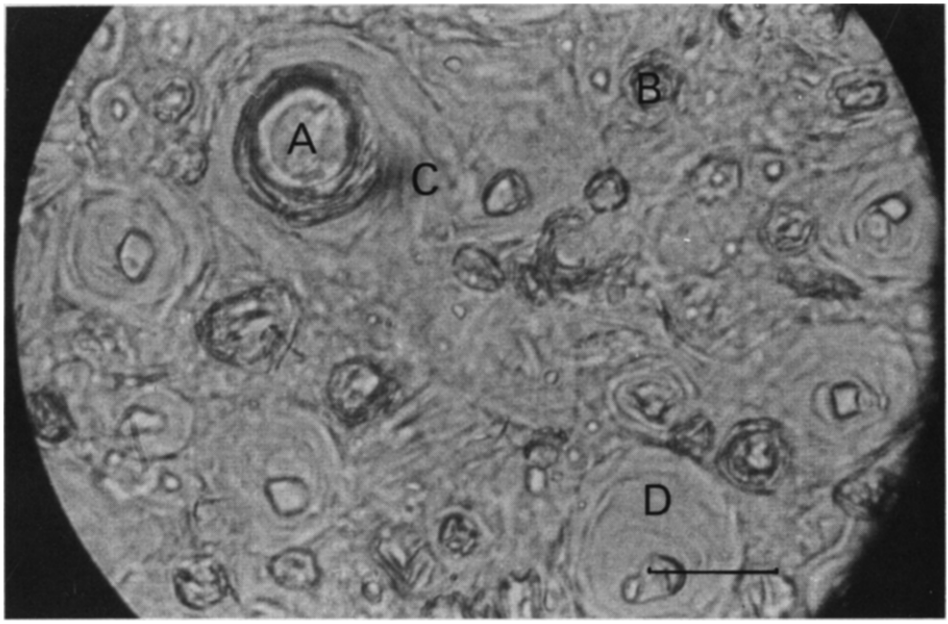


Fig. 6. Photomicrograph of the emulsion E_1 containing 5% w/w liquid paraffin. 1 division = 20 μm.

w/w cetostearyl alcohol. Similar graphs of the ratio of the peak heights at 2840, 2880 and 2925 cm^{-1} are also non-linear (Fig. 3) and even here three distinct phases in the curves between 0–1%, 1–4% and > 4% can be easily identified. These phase changes are consistent with the changes that occur in both the opacity (Rowe and Patel, 1985) and the structure (Patel et al., 1985a) of these gel systems. At concentrations below 1% w/w cetostearyl alcohol the gels are vesicular in structure with low scattering indices, at between 2 and 4% the vesicles coexist with a developing lyotropic liquid crystalline phase centred around some excess unreacted cetostearyl alcohol while at concentrations above 4% w/w cetostearyl alcohol there is a well-developed lyotropic liquid crystalline phase with a vast excess of cetostearyl alcohol particles.

Fig. 5 shows the spectra at wave numbers in excess of 2700 cm^{-1} for the features

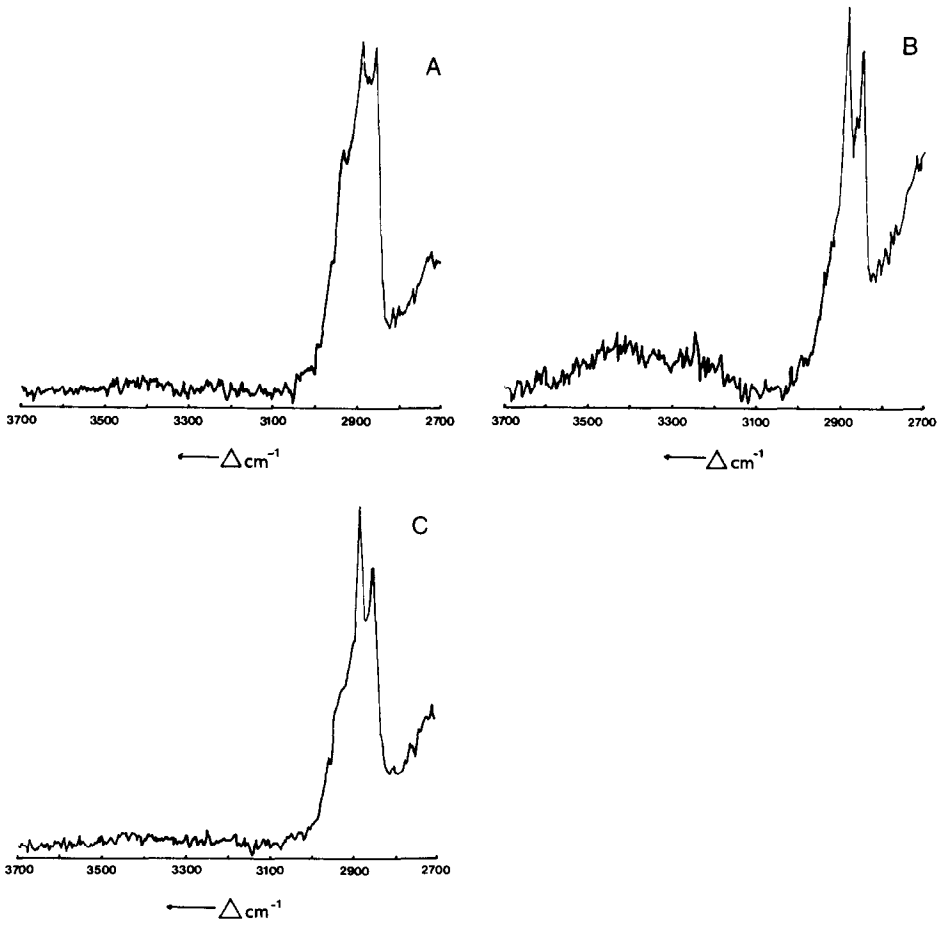


Fig. 7. Raman spectra of the features A, B and C annotated in Fig. 6.

annotated A, B, C and D in the photomicrograph of the ternary gel T_8 prepared with 10% w/w cetostearyl alcohol (Fig. 4). The spectra of the polyhedral shaped features A and B are virtually identical to the reference spectra obtained for cetostearyl alcohol (Fig. 1A). The spectra for the features C and D believed to be the lyotropic liquid crystalline phase (Patel et al., 1985a) also show peaks indicative of the presence of cetosteary alcohol although these features show the broad band between 3100 and 3600 cm^{-1} indicative of the presence of water. The ratio of the peak heights at 2840 and 2880 cm^{-1} in the case of features C and D are higher (approximately 0.90) compared to that for the features A and B (approximately 0.75) indicative of the presence of a small amount of cetrimide.

Fig. 7 shows the spectra from features annotated A, B and C in the photomicrograph of the emulsion containing 5% w/w liquid paraffin (Fig. 6). Features B and C show similar spectra to the features C and D and A and B, respectively, in the ternary gel; i.e. the lyotropic liquid crystalline phase consisting primarily of cetostearyl alcohol with a trace of cetrimide and the excess cetostearyl alcohol respectively. The spectra for the spherical feature—believed to be a droplet of liquid paraffin— is not unlike the reference spectra for liquid paraffin with the exception that there is less of a peak at 2925 cm^{-1} and a more pronounced peak at 2880 cm^{-1}. Since in the preparation of the emulsion system the cetostearyl alcohol is initially dissolved in the liquid paraffin these small differences in the spectra can be interpreted as being due to the presence of cetostearyl alcohol within the droplets. Confirmation of this was obtained in two ways, firstly by examining the spectra of a bulk sample of liquid paraffin containing 0.5% w/w cetostearyl alcohol (Fig. 8) and secondly by the use of the computer to simulate the spectra of mixtures of the two components (Fig. 9). Both show the changes in the liquid paraffin spectra, i.e. the decrease in the peak at 2925 cm^{-1} with the corresponding increase in the peak at 2880 cm^{-1} seen in feature A.

The spectra obtained for the lyotropic liquid crystalline phase in both the emulsion and gel indicating that cetostearyl alcohol is by far the major component is

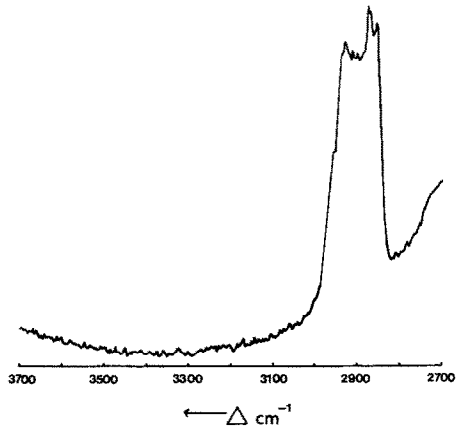


Fig. 8. Raman spectra of liquid paraffin containing 0.5% w/w cetostearyl alcohol.

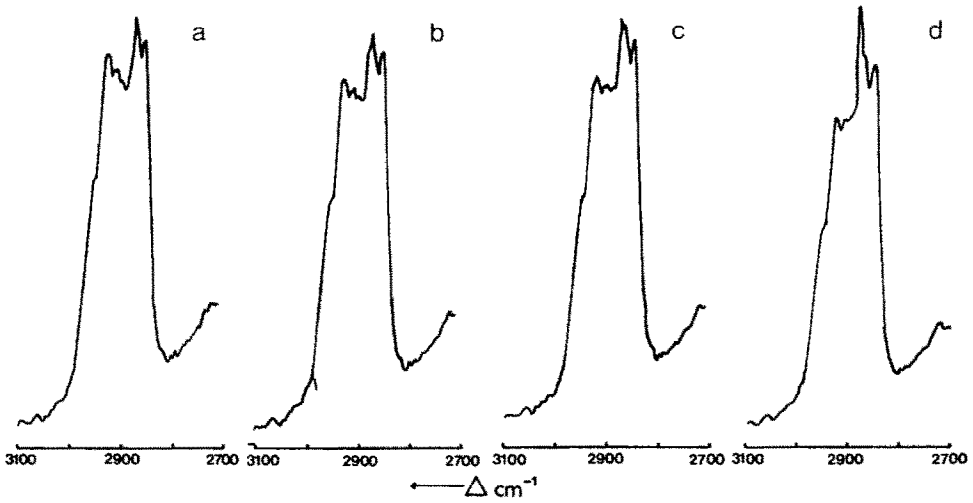


Fig. 9. Simulated Raman spectra of liquid paraffin containing different ratios of cetostearyl alcohol. (a) 1:0.015; (b) 1:0.125; (c) 1:0.25; (d) 1:0.5.

not inconsistent with more recent data obtained on the analysis of the bulk water phase of these systems indicating the presence in this phase of at least 70–80% of the theoretical free cetrimide (Patel et al., 1985b). Unfortunately, in both systems, it was difficult to obtain spectra in the finger-print region for the liquid crystalline phase due to the movement of the sample during overnight accumulation on the mono-channel detection scanning system as this would have been useful in confirming or repudiating the presence of cetrimide in this phase. It was also difficult to identify a bulk water phase in the samples when examined under the microscope.

The results certainly show the potential of this relatively rapid, non-destructive technique in the analysis of dispersed systems such as gels and emulsions. Although the spectra have been interpreted qualitatively, there does appear scope for some quantification of the data, especially in the determination of the amount of cetostearyl alcohol present in the droplets of the liquid paraffin in the emulsion and in the determination of the actual molar ratio of the cetostearyl alcohol/cetrimide present in the lyotropic liquid crystalline network.

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