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Variation in Cetostearyl Alcohol and Lecithin from Different Sources: Evaluation by Dielectric Analysis

R. C. ROWE

Zeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire, SK10 2NA, UK

Abstract

Dielectric analysis has been used to evaluate the variation with source of both cetostearyl alcohol (when used in aqueous gels prepared with cetostearyl alcohol and cetrimide) and lecithin (when used in oil-in-water emulsions).

In both examples differences in the dielectric response were detected for samples prepared using excipients from different sources, despite the failure of other tests to detect any difference.

The differences seen could be related to changes in the structures of the samples.

Dielectric analysis in the low-frequency range (below 10^4 Hz) has proved useful in the characterization of heterogeneous pharmaceutical gels (Dissado et al 1987; Rowe et al 1988) and of emulsions (Hill et al 1990). Unlike most other techniques used for the examination of such systems, dielectric analysis is performed on the sample in its normal, as prepared, state making it particularly useful for observing and monitoring processes that can lead to deterioration of the product, specifically on storage. In addition to specific structural analysis, Craig (1995) has also suggested the technique be used as a quality-control tool whereby any deviations from the measured response of a standard reference sample would indicate a fault in the product. Clearly this vision can be taken further, specifically in the investigation of both batch and source (manufacturer) of excipients used in the manufacture of the product. In this case deviations from the measured response of the reference sample would indicate a variation in the functionality of the excipient. In this paper this concept has been evaluated in two case studies involving the variation with source of, firstly, cetostearyl alcohol used in the preparation of a gel and, secondly, lecithin used in the preparation of an oil-in-water emulsion.

Materials and Methods

Gels were prepared containing 10% cetostearyl alcohol (from two sources) and 0·5% cetrimide. The cetostearyl alcohol at 80°C was dispersed in the aqueous cetrimide solution at the same temperature and stirred gently with a paddle stirrer for 1 h before being left to cool to approximately 60°C. The dispersion was then homogenized by use of a Silverson multipurpose high-speed mixer for 15 min or until the setting point of the gel was reached. The gel was then left to cool to room temperature where it was stored for at least 2 weeks before being tested. Both samples had viscosities (measured at a shear rate of 150 s^{-1} using a Rotovisio RV12 Viscometer from Haake Mess-Technik, Karlsruhe, Germany) of between 1·0–1·4 Pa s.

Emulsions were prepared by mixing the oil phase (soybean oil, 10·0% w/w, lecithin (from two sources), 1·2% w/w, and a substituted phenol, 1·0% w/w) and the aqueous phase (glycerol, 2·25% w/w, NaOH and distilled water) with a high-shear mixer and then homogenizing for 10 min by use of a high-pressure homogenizer (Manton Gaulin, model 15M). All processing was performed under nitrogen at 70°C. The emulsions were transferred to 15-mL ampoules under nitrogen; the ampoules were sealed and then sterilized in an autoclave. Both emulsions had a mean globule size (measured using photon-correlation spectroscopy) of between 0·21 and 0·24 μm.

The dielectric response of both systems was measured using a frequency-response analyser in the frequency range 10^{-2} to 10^4 Hz. The analyser was computer-controlled and measured at four frequencies per decade. For the gel a plane parallel cell with platinum electrodes was used; for the emulsion a special cell that could be flushed with nitrogen was constructed (Hill et al 1990). Both cells were mounted in a temperature-controlled cryostat. All results were plotted in terms of capacitance and loss as a function of frequency using log–log scales (Dissado et al 1987).

Results

Dielectric responses for the two gels are shown in Fig. 1. If the response for the gel prepared from cetostearyl alcohol obtained from the first source (i.e. material obtained from a synthetic source) is regarded as the standard, then the response for the gel prepared from cetostearyl alcohol obtained from the second source (i.e. the material obtained from a marine source) deviates significantly in the mid- and high-frequency ranges. This response can be interpreted in terms of changes in the gel structure only because extensive background work had previously been performed (Dissado et al 1987). The gels have a complex structure consisting of crystalline particles of cetostearyl alcohol acting as nucleating centres for a network of cetostearyl alcohol bilayers swollen with water which extends throughout the system (Patel et al 1985). For such a system the dielectric response might be interpreted (Dissado et al 1987) in terms of five processes, four bulk processes (associated with water and the cetrimide) in series with a barrier response (associated with the bilayers). The differences seen between the dielectric responses for the two gels prepared from the cetostearyl alcohol from two sources can therefore be inter-

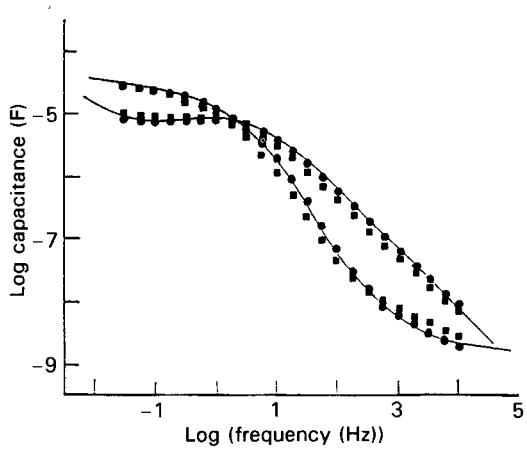

FIG. 1. The dielectric response of gels prepared from cetostearyl alcohol from the synthetic source (●) and the marine source (■).

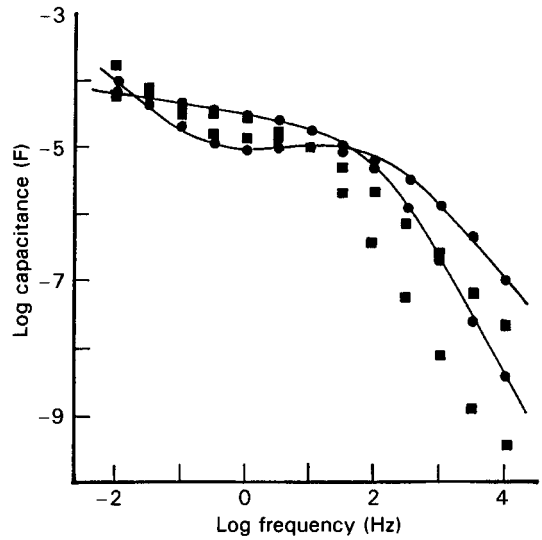

FIG. 2. The dielectric response of emulsions prepared from lecithin from the synthetic source (●) and the marine source (■).

preted in terms of changes in the bulk responses as a result of cetrimide ions present between the bilayers of the cetostearyl alcohol. The gel sample prepared from cetostearyl alcohol from the marine source shows more evidence of these processes, suggesting the presence of a more structured system.

Dielectric responses for the two emulsion samples are shown in Fig. 2. The response for the emulsion prepared from lecithin from the second source shows significant differences across the whole frequency range with very large differences at frequencies in excess of 10 Hz. Extensive work on this emulsion system (Hill et al 1990) has shown that the dielectric response observed can be characterized in terms of a high-frequency response, related to the bulk of the emulsion, and a low-frequency response related to the oil–water interface. These responses can be characterized further in terms of a bulk conductance and a barrier conductance and capacitance, the barrier conductance and capacitance being related to the packing of the lecithin molecules at the interface. The emulsion prepared from the lecithin from the second source has smaller bulk conductance, a similar barrier capacitance but a larger barrier conductance. This would imply a less compact, more porous interface.

The results clearly show that dielectric analysis can be used to detect variation in excipients from different sources. However, an interpretation of the dielectric response in terms of product structure is necessary otherwise the results would be meaningless. Clearly, this background work does involve a large resource in time and effort and might be difficult to justify in an industrial environment. However, for complex systems, for which there are few, if any, analytical techniques that can be applied to study structure in the normal, as prepared, state, it would be expected that this background work would have been performed as part of the formulation exercise. In these circumstances dielectric analysis for evaluating variation of specific important excipients from different sources would be an attractive proposition. Clearly, an experiment involving a frequency scan is necessary (one-point analysis is obviously not satisfactory), and this does take time. However, once the sample is set up, the experiment is computer-controlled and involves little human input.

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