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The use of low frequency dielectric analysis in the characterisation of metered dose inhaler formulations

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Abstract

The use of low frequency dielectric spectroscopy as a novel means of studying metered dose inhaler preparations is described using a simple model system comprising a propellant (Propellant 113, 1,1,2-trichlorotrifluoroethane), a drug (salbutamol sulphate) and a surfactant (sorbitan trioleate). The dielectric spectrum of Propellant 113 was obtained over a frequency range of 10^{-2}–10^{4}Hz and was shown to exhibit a small increase in capacitance but no discernible increase in conductivity compared to the empty cell. Addition of 1% w/w salbutamol sulphate did not result in a significant change in response. Measurement of the response of sorbitan trioleate (0.05–5% w/w) in Propellant 113 showed a concentration dependent increase in conductivity. However, this conductivity was shown to decrease in the presence of 1% w/w drug, implying that the surfactant was adsorbed onto the surface of the drug. Furthermore, the decrease was most marked for lower surfactant concentrations, with an inflexion in the conductivity/concentration curve being observed between approx. 0.5 and 1% w/w surfactant. This correlates with particle size analysis data which showed evidence for aggregation of drug particles at surfactant concentrations up to approximately 0.3%–0.5% w/w. Therefore, the study implies that dielectric analysis may be used as a means of monitoring the adsorption of surfactant onto the surface of drug particles in metered dose inhaler formulations, thereby representing a novel means of characterising these systems in situ.

Keywords: Aerosol; Conductivity; Dielectric; Metered dose inhaler; Salbutamol; Sorbitan trioleate; Surfactant

Metered dose inhalers (MDIs) are currently the most frequently employed dosage form for drug delivery to the respiratory tract. Current formulations are predominantly suspensions of micronised active compounds in liquefied chlorofluorocarbons (CFCs). Surfactants are included in these formulations to prevent particle aggregation, ensuring uniformity of dosing on actuation of devices. The nature of surfactant-propellant-particle interactions are poorly understood, although recent studies have suggested that the electrical properties of the suspended particles, and their modification in the presence of surfactants, are fundamental to the behaviour of the system (Byron, 1990; Wyatt and Vincent, 1992; Clarke et al., 1993). A clearer understanding of the interactions between particles and surfactants in propellant based systems is clearly desirable, particularly since currently used surfactants are

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poorly soluble in the propellants being investigated as possible replacements for CFCs (Dalby et al., 1990). Furthermore, since these alternative propellants are highly volatile, a system for determining such interactions in a pressurised system, in which propellants can be liquefied, would also be advantageous.

This report describes the use of low frequency dielectric spectroscopy as a means of analysing CFC systems, particularly with a view to understanding the effect of surfactant inclusion and the effect of adding drug in suspended form to that system. The technique offers the potential of studying relatively complex formulations under conditions of elevated pressure as encountered within the MDI canister.

Dielectric analysis involves the measurement of the electrical properties of a sample, from which information on the structure and behaviour of that material may be obtained. While the technique is well established in such fields as semiconductor design and polymer science, the method is relatively new to the pharmaceutical sciences. A detailed description of the technique may be found in a number of texts (e.g., Hill and Jonscher, 1983; Craig, 1992). The application of an electric field to a sample will result in the polarisation of that material, as the dipoles orientate themselves in the direction of the field. When an alternating signal is applied, the charges within the system will attempt to reorientate at the same rate as the fluctuation in the field. The system will compensate for the changes in field direction by a number of mechanisms, including reorientation and charge-hopping. The overall effect will be the movement of charge within the sample, thus generating a polarisation current (P). The relationship between the polarisation and the applied field (E) at any frequency (ω) will be given by:

$$P(\omega) = \chi(\omega) \cdot E(\omega) \tag{1}$$

The term which relates the polarisation to the magnitude of the applied field is the susceptibility (χ). This parameter is an intrinsic property of the sample and, for an alternating field, must be considered in terms of both magnitude and phase angle with respect to the applied field. Consequently, χ may be expressed as a complex number, i.e.

$$\chi^*(\chi) = \chi'(\omega) - i\chi''(\omega) \tag{2}$$

where i is the square root of -1 and χ' and χ'' represent the real (energy storage) and imaginary (energy loss) components of the susceptibility, respectively. In practice, these parameters are most easily measured in terms of the capacitance (C) and dielectric loss (G/ω, where G is the conductance) which are related to the real and imaginary susceptibilities respectively by:

$$C = (\epsilon_0 A/d) \cdot [\chi'(\omega) + \epsilon(\infty)] \tag{3}$$

and

$$G/\omega = (\epsilon_0 A/d) \cdot \chi''(\omega) \tag{4}$$

where ϵ_0 is the permittivity of free space and $\epsilon(\infty)$ denotes the permittivity at infinite frequency.

In this case, the conductance G reflects the movement of charge due to reorientation of fixed dipoles, rather than free movement of charge from one electrode to another, the former being known as a.c. conductance and the latter as d.c. As both processes may take place within the same sample, Eq. 4 may be written as:

$$G/\omega = (\epsilon_0 A/d) \cdot \chi''(\omega) + G_{\text{d.c.}}/\omega \tag{5}$$

The a.c. conductivity is generally observed in the MHz and higher frequency regions, hence at lower frequencies (i.e., kHz and below), the dielectric loss may be dominated by the d.c. component. Furthermore, if the d.c. conductivity is itself low, this response may only be observed in the sub-Hz frequency range, as the dielectric loss (G/ω) may only become measurable when ω is low. Consequently, it is necessary to have equipment which is capable of measuring down to extremely low frequencies in order to measure very small conductivities. In this study, the use of low frequency dielectric spectroscopy as a means of studying the very small responses associated with CFC systems will be outlined.

1,1,2-Trichlorotrifluoroethane (Propellant 113, P113, Sigma), sorbitan trioleate (Sigma) and micronised salbutamol sulphate (Norton Healthcare) were used as received. Systems under exam-

ination included P113 alone, a suspension of 1% w/w salbutamol sulphate in P113, solutions of up to 5% w/w sorbitan trioleate in P113 and both 1% w/w salbutamol sulphate and various concentrations of surfactant in P113. The systems were sonicated in a water bath (Decon Ultrasonic Ltd) for 5 min to ensure dispersion or dissolution of the components.

Samples were analysed by low frequency dielectric spectroscopy using the following conditions. Approx. 3 ml of sample were poured into a stainless-steel cell (Craig et al., 1993) consisting of two platinum electrodes (area 0.5 cm^2 and separation distance 1 mm). The cell was sealed to prevent evaporation of the solvent during the measurements. All samples containing drug were sonicated for 5 min prior to testing. A voltage of 0.1 V_{rms} was applied and the response measured at 298 K over a frequency range of 10^4–10^{-2} Hz. The equipment automatically measures the sample at least three times to give an average value with a coefficient of variation within 5%. All studies were repeated with freshly prepared samples and superimposible spectra were obtained in each case. The mass median diameter and size distribution of salbutamol sulphate suspended in propellant and propellant-surfactant mixes was measured by laser diffraction (Malvern 2600c, Malvern Instruments, Malvern, U.K.) fitted with a 63 mm lens. A coefficient of variation $< 3\%$ was found in all cases.

Fig. 1 shows the response of P113 alone and in the presence of salbutamol sulphate compared to that of the empty cell. The response exhibits a flat capacitance over the majority of the frequencies studies, while the dielectric loss shows an increase at the lowest frequencies studied. In this case, the capacitance may be considered to represent the dielectric constant ϵ_R, which is given by

$$\epsilon_R = C/C_0 \quad (6)$$

where C is the capacitance of the sample and C_0 represents the capacitance of the empty cell. This value is usually obtained by measuring the capacitance of a sample in the kHz region, in which the magnitude of this value is assumed to be constant. The spectra show this assumption to be accurate in this case. No significant changes in C

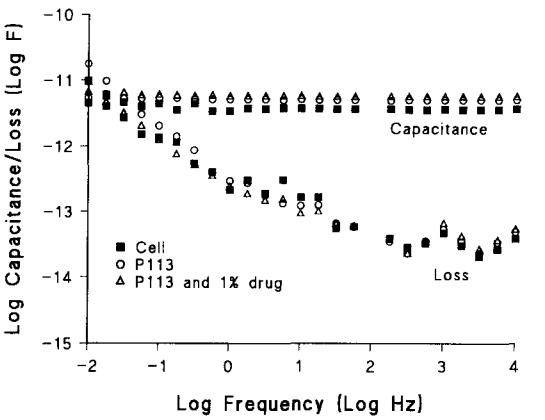

Fig. 1. Dielectric response of P113 in the presence of salbutamol sulphate.

were observed on addition of the drug. The dielectric loss of the empty cell showed an increase on lowering the frequency to the sub-Hz range which corresponds to the conductivity of the insulation material of the cell itself, these values being approx. 6 orders of magnitude less than those expected for a polar liquid such as water. These values are approaching the limit of sensitivity of the instrument, resulting in the response being somewhat noisy. There was a slight increase in loss on addition of P113, although given the noise observed in this region it is not appropriate to interpret the results further.

On addition of surfactant, a marked increase in low frequency loss was seen (Fig. 2), reflecting either the charge carrying properties of the more

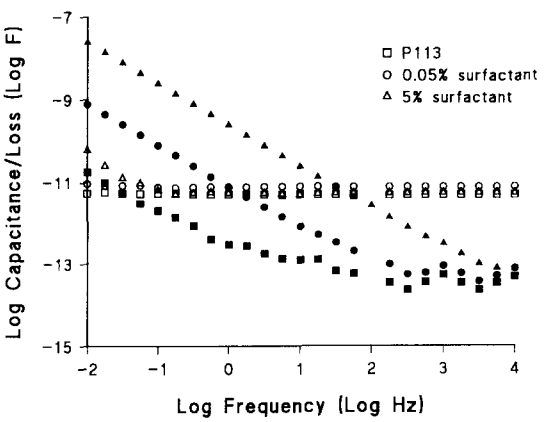

Fig. 2. Dielectric response of sorbitan trioleate in P113. Clear symbols represent capacitance; shaded symbols represent dielectric loss.

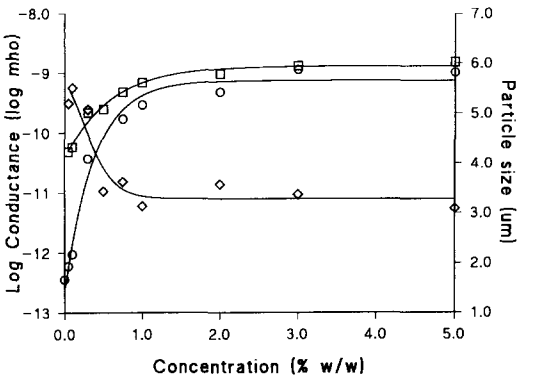

Fig. 3. Conductance of sorbitan trioleate in P113 at 0.01 Hz in the presence and absence of 1% salbutamol sulphate, compared to the measured particle size of salbutamol sulphate. (□) Conductance of sorbitan trioleate in P113; (○) conductance of sorbitan trioleate in P113 in the presence of 1% salbutamol sulphate; (◇) particle size of salbutamol sulphate.

polar surfactant molecules or trace impurities within the surfactant (or both). The increase is clearly concentration dependent, as shown in Fig. 3. The discontinuity seen in the profile may be associated with the formation of micelles, although more work is required in order to confirm this. However, it is interesting to note firstly that the technique is sensitive to the presence of relatively small quantities of surfactant (0.05% w/w) and secondly that the technique is more sensitive to changes in surfactant concentration at lower sorbitan trioleate levels. This therefore gives some indication of the sensitivity of low frequency dielectric spectroscopy to the addition of polar materials to non-polar liquids.

On addition of the drug to a low concentration surfactant solution, the dielectric loss showed a marked decrease to a value similar to that of P113 alone. This may be interpreted in terms of the surfactant being adsorbed onto the surface of the particles, hence these molecules are no longer contributing to the dielectric loss. However, addition of the drug to more concentrated solutions of surfactant had a much smaller effect. It is therefore reasonable to suggest that the surface of the particles becomes saturated at these concentrations, leaving sufficient quantities of free surfactant to allow a high response to be observed. The concentration dependence of this effect is shown in Fig. 3. Clearly, a greater decrease is seen at lower surfactant concentrations, as a greater proportion of the added surfactant is adsorbed onto the particle surface when less sorbitan trioleate is available initially. Furthermore, the measured particle size of the drug decreases on adding surfactant due to the improved wetting of the particles resulting in greater wettability and decreased aggregation (Fig. 3), with a reasonable correlation being observed between the inflexions seen in the conductance and particle size curves.

The study therefore demonstrates that low frequency dielectric spectroscopy may be used to study the adsorption of surfactants onto drug particles in MDI aerosol formulations. This represents a novel approach to the study of aerosol preparations and the data suggest that it should be possible to directly measure the concentration of free surfactant remaining in the propellant, thereby allowing adsorption isotherms to be obtained. While propellant P113 is not pharmaceutically important in itself, the study clearly demonstrates the potential of this type of measurement. As the dielectric cell need only consist of two electrodes immersed in the sample, there is no reason why the same principal could not be applied to pressurised aerosols, once a suitable cell has been constructed. This would then allow direct monitoring of these dosage forms in a non-invasive manner, thereby considerably enhancing our understanding of the behaviour of MDI preparations.

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