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APPLICATIONS OF LOW FREQUENCY DIELECTRIC SPECTROSCOPY TO THE PHARMACEUTICAL SCIENCES

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ABSTRACT

Low frequency dielectric spectroscopy (LFDS) is an analytical technique which has found considerable application in the study of pharmaceutical systems. In this article, an outline of the theoretical and practical aspects of the method will be given, as well as a discussion of the advantages and disadvantages of the technique. Examples will be given of how LFDS may be used in the analysis of pharmaceutical systems, including studies on solid dispersions, inter-batch variation, liposome suspensions and cyclodextrins.

INTRODUCTION

Dielectric spectroscopy involves the measurement of the electrical properties of a material, from which information on the structure and behaviour of that system may be extrapolated. The method is used in such fields as semi-conductor design[1,2], polymer science[3] and colloid and emulsion science [4]. Furthermore, dielectric analysis is coming to be recognized as being applicable to pharmaceutical

materials, particularly for multicomponent or other complex systems to which many other techniques are inapplicable. In this article, an introduction to general dielectric analysis will be given, along with examples of how the technique may be of use in the study of pharmaceutical systems. However, it should be emphasised that because dielectric behaviour may be studied over a wide range of frequencies, there are a number of different techniques available. The principles of all dielectric techniques are largely similar, the differences lying in the type of relaxation processes seen over the various frequency ranges. This article is therefore not intended as a comprehensive review but rather as an introduction to one method of dielectric analysis, namely the measurement of the low frequency response.

Theory of dielectric spectroscopy

A dielectric can be defined as a material which contains dipoles, i.e. regions of charge separation characterised by a dipole moment μ, where

$$\mu = ql \qquad \text{Eq.1}$$

The charge and separation distance are given by q and l respectively. On subjecting a dielectric to an electric field, the sample will respond so as to maintain overall neutrality.

The process by which charge is neutralised on the plates is known as polarisation. The polarisation (P) may be described by

$$P = (\epsilon_r - 1).\epsilon_0 E \qquad \text{Eq.2}$$

where E is the field strength, ϵ_0 is the permittivity of free space ($8.85 \times 10^{-12} Fm^{-1}$) and ϵ_r is the relative permittivity, also known as the dielectric constant. The permittivity is therefore a measure of

the ease with which a sample polarises and is an intrinsic property of the material under study.

When an alternating field is applied, dipoles will attempt to reorientate with the changes in the field direction. However, due to the inertia of the dipoles themselves and restrictions imposed by the surrounding environment, a phase difference develops between the field and the polarisation. The response of the sample may therefore be described by two parameters; the magnitude of the response and the phase relationship between the stimulus (i.e. the field) and that response. This duality is most easily expressed by considering the relative permittivity to be a complex number, i.e.

$$\epsilon_r^* = \epsilon_r' - i\epsilon_r'' \qquad \text{Eq.3}$$

where i is the square root of -1. The real (ϵ_r') and imaginary (ϵ_r'') parameters represent the out of phase and in phase components of the polarisation with respect to the applied field.

However, it is not possible to measure the real and imaginary permittivities directly, as they are intrinsic parameters while the measured response will invariably depend on sample size. It is therefore more convenient to express these components in terms of measured parameters. One method of doing this is to describe the response in terms of the capacitance (C) and dielectric loss (G/ω, where G is the conductance and ω is the frequency of measurement). These two may be related to the real and imaginary permittivities by

$$C = \frac{A.(\epsilon_r'\epsilon_0 + \epsilon^\infty)}{d} \qquad \text{Eq.4}$$

and

$$G/\omega = \frac{\epsilon_r''\epsilon_0 A}{d} \qquad \text{Eq.5}$$

where ϵ^∞ is the permittivity at infinite frequencies. C and G/ω may therefore measured over a range of frequencies and, as will be

shown, examination of both the absolute magnitudes of these parameters and the relationship between the two leads to information regarding the structure of the sample.

This explanation of dielectric theory is, for the purposes of brevity, somewhat incomplete as there are considerably more facets to the argument than have been presented here. While the above explanation will serve the purposes of the present article, the interested reader is referred to a number of additional texts for further details[5,6,7,8].

Methods of Dielectric Measurement

All dielectric measurements involve the application of a field to a sample and the measurement of the response of that material. However, a variety of methods are available within this broad description, the choice depending on the information the experimenter wishes to obtain. For the low frequency work described in this review, a spectrometer designed by Dielectric Instrumentation Ltd. (Worcs., UK) was used. This consists of a frequency response analyser (FRA) which produces a signal at a specified voltage and frequency. This signal is passed to the sample via an interface which contains a series of resistor-capacitor circuits, one of which is automatically selected at each frequency in order to provide a reference against which the response of a sample may be measured. The returning signal is then analyzed by the FRA and displayed in terms of C and G/ω at each frequency, both graphically and as a numerical printout. The system automatically analyzes the sample at least three times and gives the average measurement at each frequency. The frequency range available using this equipment is 10^7 Hz to 10^{-4} Hz, although in practice a range of 10^4 Hz to 10^{-2} Hz is commonly used. Each scan over the latter range takes approximately 45 minutes.

The sample cells used have been designed and built by the various investigators as there is no single cell which is suitable for all materials. The general principal, however, remains constant for all measurements. Two electrodes are placed either side of the sample, the electrode size being of the order of $1cm^2$ and the distance between the two approximately 1-5mm. It is important when designing cells to minimise the response of the cell itself. This is achieved by using insulating materials in which to mount the electrodes and by ensuring that all wiring is adequately screened. It is also important, especially when measuring solid samples, to ensure good contact between the electrodes and the sample.

Advantages and disadvantages of the technique

The electrical properties of a material are rarely of pharmaceutical interest in themselves. However, these properties may be a reflection of the structure and behaviour of the sample. For example, different crystal forms of a material may display different dielectric properties. It is therefore possible to use the technique as a means of probing the physical and chemical structure of materials. As will be shown, the technique is particularly useful for complex systems which may be difficult to analyze using conventional techniques.

Secondly, most pharmaceutical materials have dielectric properties, hence it follows that most such samples may be measured. Furthermore, the flexibility in electrode design allows a range of shapes or indeed phases to be examined. It is possible, for example, to monitor the response of a sample from the molten state through to the solid state without the need to remove that sample from the equipment. One may therefore use the technique as a means of assessing the effects of external variables such as temperature, pressure and humidity on the structure and behaviour of a sample. Software is also available which allows the response at

any particular frequency to be measured over a period of time, thus allowing kinetic studies to be performed. Finally, the technique is usually non-invasive, which is of considerable use if further tests are required on that particular piece of material.

The principal disadvantages of the technique are firstly that not all samples may be measured. Some materials, for example, have either too high a response (such as strong electrolyte solutions or metals) or too low a response (such as solid hydrocarbons). However, the majority of samples that our group have studied, from biological tissues to non-aqueous solvents, have shown responses within the measuring capability of the equipment, hence there have been few occasions whereby this problem has been apparent. A more serious problem concerns the interpretation of the data. As will be discussed shortly, the data may be used as a fingerprint, whereby results are simply compared to those obtained from samples prepared under various conditions, e.g. different temperatures, humidities, etc.. It is, however, preferable to be able to interpret each spectrum independently in terms of how the dielectric behaviour relates to the structure and behaviour of the sample. This is often, but not always possible as the use of the technique in the applied sciences is relatively new, hence at present the knowledge base for dielectric analysis is less wide than for many other more established techniques. This problem is not helped by the inaccessibility of most dielectric literature, although a monograph on dielectric analysis written specifically for pharmaceutical scientists is currently being prepared[8].

EXAMPLES OF THE USE OF LOW FREQUENCY DIELECTRIC SPECTROSCOPY (LFDS)

1) Solid dispersions

One of the first pieces of pharmaceutical work using the low frequency technique was that of Chatham[9], who examined the

structure of solid dispersions. These dosage forms involve the dispersion of a drug in a water soluble carrier such as polyethylene glycol (PEG), usually by melting a physical mixture of the drug and carrier. For reasons which are not yet fully understood, preparation of drugs in this manner may result in a considerable enhancement in drug release rate. As a general approach, the author highlighted the importance of studying the properties of the carrier alone as well as the dispersions themselves, as PEGs in the molecular weight range used for solid dispersions (3,000 to 20,000) may adopt a range of solid structures, differing in both polymorphic form and degree of crystallinity[10]. The structure is largely dependent on the thermal history of the sample, hence by altering the manufacturing conditions of the dispersion, it is possible to change the structure and hence the dissolution behaviour of the final dosage form.

The question therefore arises as to how these changes may be characterised. Conventional techniques such as X-ray diffraction and differential scanning calorimetry are of undoubted use in this respect. However, each suffers from its own associated disadvantages, hence it is useful to have further techniques available for studying these systems. One contribution to be made by LFDS concerns the capability of the technique to measure the response of systems in both the molten and solid states within the same sample cell, thus allowing the behaviour of the samples to be measured over a range of temperatures. Chatham (1985) examined the effects of thermal history of PEG 4,000 on the dielectric response and found the technique to be sensitive to changes in the PEG structure induced by the various preparation techniques. A typical molten response is shown in Figure 1, with the solid response of slow and flash cooled PEG 4,000 shown in Figure 2.

The study illustrates firstly that the technique may measure the response of a material in both the molten and solid states and secondly that changes in the solid structure of a material may be

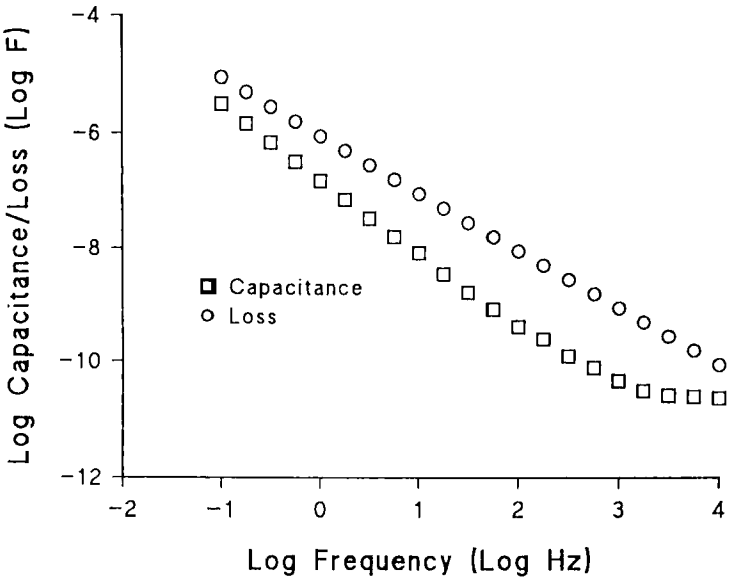

FIGURE 1

Dielectric response of molten PEG 4,000 (323K)
(reproduced with permission)

detected using LFDS. In a later study, the addition of a model drug (nortriptyline HCl) was found to increase the magnitude of the dielectric response of a range of different molecular weight PEG samples, both in the molten and solid states[11], even though the maximum temperature used was well below the melting point of the drug. This may therefore indicate dissolution of the drug in the polymer. If so, this has important implications for the study of drug dispersions within polymers in general, as it is frequenctly useful to have a knowledge of the physical state of a drug within a matrix. Furthermore, there has been growing interest in the effects of 'doping' polymers with various salts to produce conducting polymers for the production of rechargeable batteries[12], hence there is considerable overlap between the studies conducted here and

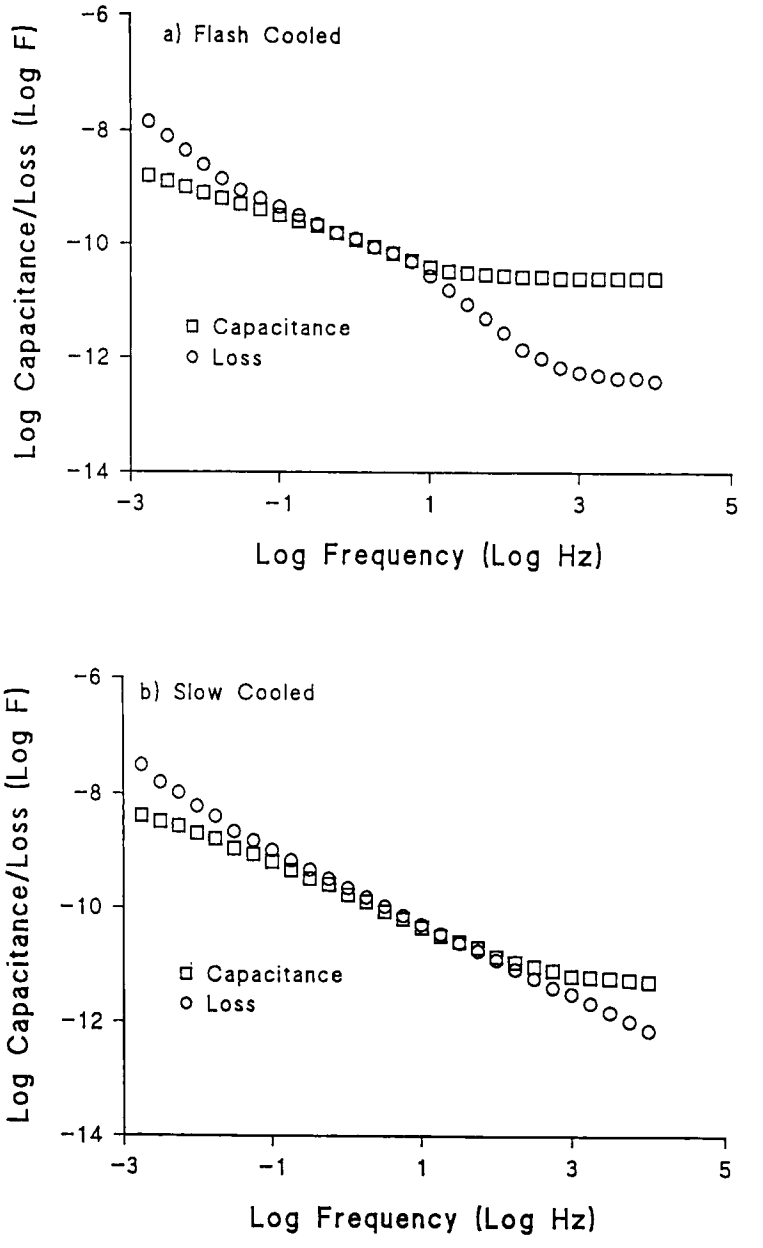

FIGURE 2

Dielectric response of solid PEG 4,000 at 293K prepared a) by flash cooling from the melt and b) by slow cooling from the melt (reproduced with permission)

considerations that are applicable to other fields. In a later study by Lievens et al[13], the authors showed that the technique could detect changes in the solid structure of drug dispersions in PVP resulting from the use of different solvents in the manufacturing process, thus further indicating the potential of the technique in the study of solid dispersions as a quality control tool.

2) Quality control of pharmaceutical excipients

In a recent study, Boyd et al[14] discussed investigations performed on a batch of direct compression lactose which was found to produce tablets with longer disintegration times than those produced using other batches. However, a range of standard techniques such as X-ray diffraction, optical microscopy and measurements of water content showed no difference between this and other batches. A subsequent study[15] demonstrated that the inter-batch variation could be detected using the dielectric technique, as shown in Figure 3. While more work is required before the exact mechanism may be identified, the study has clear implications for the use of the technique as a batch screening process.

3) Study of liposome systems

Investigations by Barker et al[16] have been performed on liposome suspensions containing dipalmitoylphosphatidylcholine (DPPC). This work was conducted with a view to testing a theory outlined by Hill and Pickup[17] in which the authors suggested that for many aqueous disperse systems the behaviour of the aqueous phase of the sample is seen at high frequencies (10^2 Hz to 10^4 Hz) while at lower frequencies (less than approximately 1 Hz) the spectra correspond to thin layers present within the sample. In the case of liposomes it was therefore suggested that the high frequency response would reflect the bulk behaviour of the liposome suspension and the low

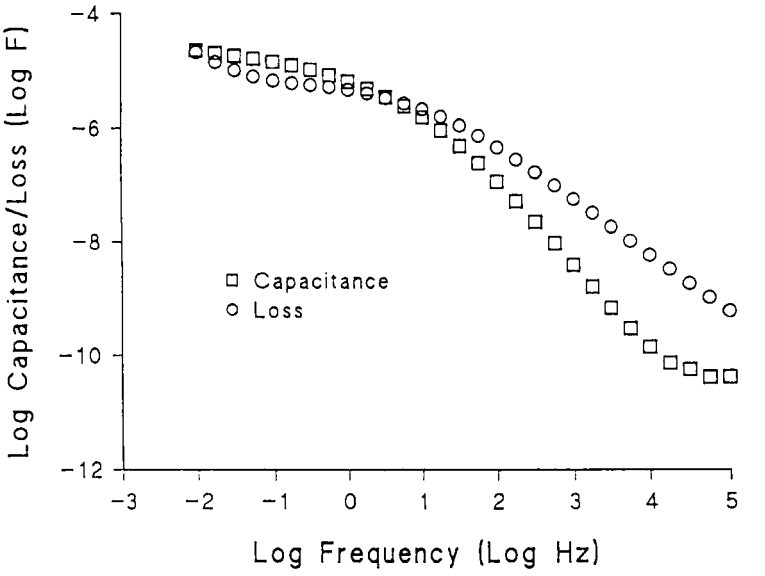

FIGURE 3

Dielectric response of direct compression lactose samples (reproduced with permission)

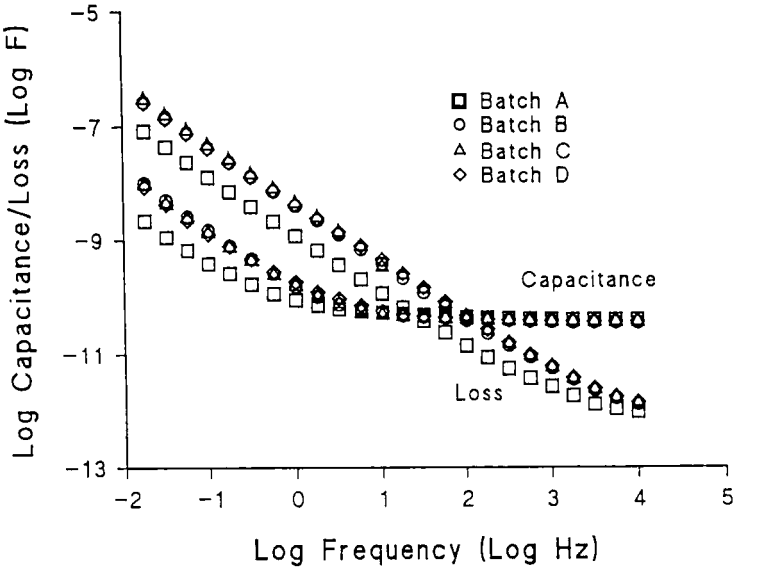

FIGURE 4

Dielectric response of DPPC in water (25mg/ml) at 298K (reproduced with permission)

frequency response would indicate the structure of the lipid bilayer. Barker et al[16] tested this hypothesis by preparing multilamellar liposomes containing DPPC and cholesterol in varying proportions using a total lipid concentration of 25mg/ml. The response for DDPC alone is shown in Figure 4. The spectra may be considered to consist of two regions, theoretically corresponding to the lipid bilayer (below approximately 1 Hz) and the bulk suspension (above 10 Hz). Addition of cholesterol (which is water-insoluble) should therefore alter the low frequency rather than high frequency response. Not only was this found to be the case, but a linear relationship was later found between the capacitance at 10^{-2} Hz and the mole fraction of cholesterol. The high frequency response was found to remain unchanged over all compositions, as predicted by the theory[17]. In a further study on the temperature dependence of liposomes[18], the low frequency response showed a discontinuity at a temperature corresponding to the phase transition temperature of DPPC (315K). Furthermore, the magnitude of the change decreased on addition of cholesterol, thus reflecting changes in the melting characteristics previously noted by Oldfield and Chapman[19].

These results indicate that LFDS may be of use in the study of liposomes for two reasons. Firstly, it allows the lipid bilayer and bulk aqueous phase to be examined separately at any temperature. This has implications for monitoring the passage of drugs through the lipid bilayers into the bulk aqueous phase. Secondly, direct measurement of the lipid bilayer introduces several possibilities for the analysis of liposomal phospholipids. For example, the presence or absence of dissolved drug, changes in the lipid conformation and several other features should all be detectable using the technique. It should also be noted that these studies were carried out without the need to dilute the suspensions.

4) The study of ß-cyclodextrin systems using dielectric spectroscopy

The use of the technique in examining multicomponent solid samples was exploited in a study on ß-cyclodextrin/acetotoluide systems[20]. Ortho-, meta- and para-acetotoluides (ACTs) were chosen as model drugs as their complexation behaviour with ß-cyclodextrin has been characterised previously[21]. Using a number of conventional techniques, the authors concluded that there was evidence for complex formation between the ß-cyclodextrin and the para- analogue, while the ortho- and meta- ACTs showed less evidence for any such interaction. It was therefore decided that these systems would provide useful models for validation of the dielectric technique.

A characteristic spectra of solid ß-cyclodextrin was obtained, as shown in Figure 5. It was noted that a peak was seen at approximately 1 Hz. Such peaks are believed to correspond to bound charges or dipoles within a system which are undergoing reorientation. On freeze drying equimolar PABA/cyclodextrin solutions, the peak was found to disappear when ortho- or meta-PABA were used. However, the peak was not only retained but was slightly increased in amplitude when the cyclodextrin was freeze dried with para-PABA. The findings of the dielectric studies are therefore compatible with those of Jones and Parr[21], indicating that the presence of an inclusion complex between para-PABA and ß-cyclodextrin may be reflected by the dielectric behaviour. The possibility that the technique is capable of detecting solid state interactions is of importance, as it has frequently proved difficult to confirm or refute the presence of complex formation between cyclodextrins and drugs.

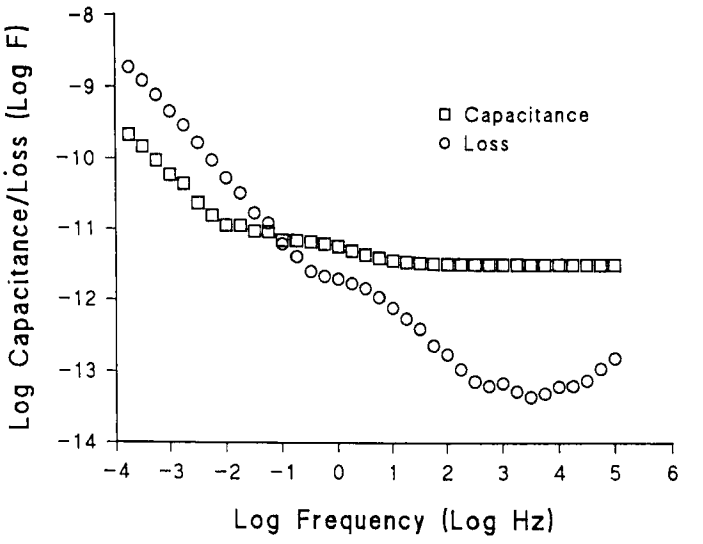

FIGURE 5

Dielectric response of solid ß-cyclodextrin (298K)
(reproduced with permission)

CONCLUSIONS

The above examples are intended to give an idea of the type of systems and problems that have been investigated using the low frequency dielectric technique. At present, a number of further studies are ongoing or are awaiting publication. These include a study of phospholipid films, tablet lubricants, structure formation by surface active agents, self-emulsifying systems, hydroxypropyl methylcellulose gels and an investigation into the effects of compaction conditions on the dielectric response of compressed powders.

There are a number of other groups using various forms of dielectric analysis to study pharmaceutical systems. While this work has not been covered here, these findings will be discussed in a future publication[8]. It is envisaged that as the knowledge base

concerning dielectric interpretation widens, the use of the technique within the pharmaceutical sciences will also expand. In this way, the considerable potential of the technique will become realised in the foreseeable future.

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