ELSEVIER

International Journal of Pharmaceutics 125 (1995) 123–132

international journal of pharmaceutics

The use of low frequency dielectric spectroscopy as a novel means of investigating the structure of pharmaceutical glyceride bases

W. Sutananta [a,1], D.Q.M. Craig [a,*], R.M. Hill [b], J.M. Newton [a]

[a] *Centre for Materials Science, The School of Pharmacy, University of London, 29–39 Brunswick Square, London WC1N 1AX, UK*
[b] *Department of Physics, Kings College London, University of London, The Strand, London WC2R 2LS, UK*

Received 18 February 1995; accepted 22 March 1995

Abstract

The dielectric responses of five glyceride bases have been assessed using low frequency dielectric spectroscopy. It was observed that each base showed different electrical behaviour. In addition, samples were either slow or fast cooled from the melt in order to change the physical structure of each material; in all cases where differences were observed, the slow cooled samples showed a greater response than fast cooled materials. The results are discussed in terms of both the movement of charges within the system and the relationship between these charge movements and the physical structure of the material. It is proposed that the differences in dielectric response between the various samples may be influenced by a number of factors, particularly chemical composition, while the differences between the responses of fast and slow cooled materials may be a reflection of segregation of the components of the bases into distinct regions. These studies indicate that dielectric analysis may be used as a novel means of characterising solid materials of pharmaceutical interest.

Keywords: Conductivity; Dielectric; Gelucire; Glyceride

1. Introduction

Gelucires are mixtures of glycerides and polyethylene glycol esters of fatty acids which may be used as bases for controlled release dosage forms (Craig, 1995a). The structural complexity of these materials renders their physical characterisation difficult, although a number of techniques such as differential scanning calorimetry, hot stage microscopy and polarising light microscopy have been used to assess the bases (Sutananta et al., 1994a,b). There is a considerable need to understand the physical structure of the Gelucires as this parameter has been shown to be related to product performance, particularly in terms of drug release rate (Sutananta et al., 1995a,b).

In this study, the technique of low frequency dielectric spectroscopy has been used as a novel means of characterising the physical structure of the Gelucires. This technique has been used for a

---

[*] Corresponding author.

[1] Present address: Faculty of Pharmacy, Silpakorn University, Sanamchan Palace, Nakornpathom 73000, Thailand.

SSDI 0378-5173(95)00129-8

number of pharmaceutical applications (Craig, 1995b) and, while there is still a need to explore the detailed interpretation of the dielectric results, the technique has demonstrated considerable potential as a means of characterising pharmaceutical systems. In order to provide the necessary context for subsequent discussions, the theory of dielectric analysis and the uses of the techniques in the study of glycerides are discussed below.

1.1. Theory of dielectric analysis

Dielectric analysis involves the measurement of the response of a sample to an applied electric field. As most samples (and virtually all pharmaceutical materials) contain dipoles, the response may be considered to be a combination of two processes; rearrangement of dipoles so as to orientate themselves in the direction of the field and charge movement through the system via conduction processes. When the applied field is alternating, the magnitude of the dipolar processes becomes frequency dependent, hence by scanning the sample over a range of frequencies it is possible to obtain a spectrum, from which information regarding the structure and behaviour of the sample may be obtained.

Using the simplest scenario of a reorientating (relaxing) dipole in an alternating field, the movement of the dipole will not keep up with the changes in field direction over the total frequency range, hence it is useful to express the response at any frequency in terms of an in-phase and out-of-phase component, in the same way that viscoelastic materials are described by storage (G') and loss (G'') moduli. In dielectric analysis, this may be expressed in terms of the permittivity of the sample at any frequency. The permittivity (ϵ) relates the magnitude of the response (polarisation) to the magnitude of the applied field and hence is an intrinsic parameter of the material under study. The permittivity at any frequency, $\epsilon(\omega)$ is given by

$$\epsilon(\omega) = \chi(\omega) + \epsilon(\infty) \tag{1}$$

and

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

where i is the square root of -1, $\epsilon(\infty)$ represents the permittivity at infinite frequency and $\chi(\omega)$ is the complex susceptibility of the polarizable sample that is being examined with the a.c. field of frequency ω. This parameter is related to the permittivity by the relationship shown in Eq. 1. The complex form of the susceptibility arises from the relative phase response of the sample. The real part ($\chi'(\omega)$) is out of phase with the applied voltage and draws no power from the source, hence this component is related to the energy stored within the system. The imaginary or loss component ($\chi''(\omega)$) is in phase, resulting in energy loss from the system.

In practice, the dielectric response of a sample is measured in a capacitance cell (at least at low frequencies), conventionally consisting of two electrodes of parallel plate geometry of plate area A and spacing d. The oscillating field is applied to the sample over a wide range of frequency and the capacitance (C) and dielectric loss G/ω, where G is the conductance, are monitored. The real and imaginary parts of susceptibility are related to these observed parameters by Eq. 3 and 4:

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

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

where ϵ_0 is the permittivity of free space (8.854×10^{-12} F m^{-1}); ϵ_r' and ϵ_r'' are the real and imaginary parts of the relative permittivity of the sample, respectively. The relative permittivity is defined as the permittivity of the sample divided by that of free space (ϵ_0). At low (kHz) frequencies, the capacitance of many (but not all) samples tends to be constant; this capacitance divided by the capacitance of the empty cell is the dielectric constant, hence it is identical to the relative permittivity. Dielectric constants are extensively used in the pharmaceutical sciences, although it should be emphasised that the use of this term implies that the capacitance is constant in the region of measurement, which may not be the case. Indeed, dielectric constants are almost invariably obtained by measuring the capacitance at a single frequency, in which case there is no way of knowing whether this value is independent of frequency in the region of measurement.

In addition to the conductance given in Eq. 4 which relates to the charge movement due to reorientation of dipoles, a frequency-independent d.c. conductivity may also be observed if electronic or ionic free charges are present. In this case, this conductance will be seen in addition to that described in Eq. 4 and may, in liquid and some solid samples, dominate the response.

The conventional analysis of the dielectric response is based on Debye's model (single dipole relaxation time) or its variations based on a distribution of relaxation times. In these models, it is assumed that the relaxation time can be associated with the rotation of individual dipoles. The Dissado-Hill theory of relaxation, however, considers that, in addition to dipole reorientation, relaxation requires cooperative motions of the surrounding structural matrix to form a cluster response, and that there is an interaction between these clusters (Dissado and Hill, 1979; Hill and Jonscher, 1983). There is therefore still debate regarding the detailed interpretation of dielectric data.

1.2. The dielectric behaviour of glycerides

The dielectric properties of glycerides in the solid state at frequencies of 0.5–50 kHz have been investigated and correlated with X-ray diffraction and thermal data by Crowe and Smyth (1950a,b, 1951). These studies were largely involved with monitoring the change in dielectric constant (ϵ') within a wide range of temperatures, rather than monitoring the frequency dependent behaviour. Essentially, the authors found that the different polymorphic forms of glycerides such as α, β' and β had different values of dielectric constant. By scanning the values of ϵ' with temperature, they were able to identify the temperature at which the polymorphic transition occurred from the abrupt change in ϵ'. In addition, they also studied the dielectric behaviour of each polymorphic form. Parkash and Blanshard (1974) later adopted the same principle and were able to identify the five polymorphic forms of trierucin. They also suggested that the dielectric loss studies may reveal more information than the dielectric constant measurement since there were more discontinuities in their graph of loss (ϵ'') vs temperature.

Crowe and Smyth (1950a,b, 1951) reported that the α-form of 1-monoglycerides, which possesses two free hydroxyl groups near the end of the molecule and is therefore highly hydrogen bonded, had a high dielectric constant and a conductance comparable to that of liquid monoglycerides. It would appear therefore that the molecules possess freedom of movement in the solid state, probably about their long molecular axes. It was suggested that such rotational freedom offered an optimum configuration, allowing the transfer of protons along the planes of hydroxyl groups located in the crystals and hence a high conductivity. The proposed proton transfer mechanisms were similar to that occurring in long-chain alcohols which are also hydrogen bonded and possess hydroxyl groups at one end. The more stable β'-or β-forms possessed dielectric constants low enough for these molecules to be considered as non-rotators. The authors also suggested that more highly substituted glycerides exhibited little or no proton transfer due to the absence of a rotator form, even though hydroxyl groups are present.

In the kHz region of frequency, a dispersion (frequency dependence) of the dielectric constant was observed in mono-and triglycerides. Similar phenomena have been observed for long-chain alcohols and have been attributed to Maxwell-Wagner polarisation between two solid phases with different conductivities and dielectric constants. When a field is applied across an interface, the charge storage properties of the two materials will differ, hence when an alternating field is applied the interface will act in a similar manner to that of a dipole in that a region of charge separation will be established. Crowe and Smyth (1950a,b, 1951) suggested that the frequency dispersion effect may be dependent upon the size and shape of crystals due to the aforementioned Maxwell-Wagner effects. Since solid fats consist of a large number of crystals of various size and shapes, it is reasonable to suggest that Maxwell-Wagner effects may indeed be of relevance to the responses of these materials.

In addition to the response of the glycerides, it is also helpful to consider the response of the polyethylene glycol (PEG) esters and trace impurities that may be found in Gelucire samples, as these substances may have an effect on the dielectric response (Chapman, 1962). Apart from glycerides and PEG esters, most Gelucires contain free fatty acids and glycerol as impurities. The amounts by weight of free acids calculated as C-14 equivalence are estimated to be 1.5–2% in glyceride mixtures (such as 43/01, 54/02) and less in mixtures of glycerides and PEG esters. Glycerol, which is a polar molecule (though less polar than water), may be present in quantities of approx. 0.5–1.5% w/w. In Gelucires which contain PEG esters (e.g., 50/02, 50/13), 1–8% w/w of free PEG and 0.5% w/w of water can be expected. Trace metals such as iron and zinc and alkaline impurities are present in the order of parts per million.

2. Materials and methods

2.1. Sample preparation

Gelucires 43/01, 50/02, 54/02, 50/13 and 55/18 (Gattefosse s.a.) were used as received. The first number of the Gelucires refers to the approximate melting point (°C) of the base and the second to the HLB value. Samples were moulded into flat-faced tablets of diameter 1.25 cm and height 0.40–0.42 cm, as previously described (Sutananta et al., 1994a). The tablets were either slow cooled at 10°C/h from 75°C or left to cool under ambient conditions (henceforth referred to as slow and fast cooled samples) in order to allow comparison between samples of different physical structure. The top and bottom sides of the tablets were coated with conducting silver loaded epoxy, enabling electrical contact to be made to the tablet surfaces, hence the coated sides acted as electrodes. The silver loaded epoxy (RS Components, Northants) contains epoxy resin and a polyamide complex as a hardener. After the wiring, the tablet was kept for 24 h in the cabinet over silica gel so that the epoxy could harden.

2.2. Dielectric measurement

Dielectric measurements were performed using the system supplied by Dielectric Instrumentation Ltd (Worcs.). An alternating field was generated by a frequency response analyser (FRA; Solatron, London) and passed through the sample via a Chelsea Interface. The returning signal was analysed by the FRA to allow the calculation of the capacitance (C) and loss (G/ω). The FRA is connected online to the computer and thus the results were automatically calculated. A plot of log C and log G/ω vs log frequency was produced together with a data printout. Preliminary studies suggested that a minimum potential that gave a good, noise-free signal was a 0.1 V r.m.s. signal for Gelucire 55/18 and 50/13 and a 1 V r.m.s. signal for Gelucires 43/01, 50/02 and 54/02.

The dielectric responses of the samples were measured at 20°C at 5% relative humidity over the frequency range of 10^5–10^{-3} Hz. At each frequency, the dielectric response was automatically measured at least three times. The temperature and humidity was controlled by placing the sample (and the measuring box) in a humidity-controlled oven. At least two tablets were measured for each sample. Excellent reproducibility was found in each case.

3. Results

Fig. 1–5 show the dielectric responses of the various Gelucires and Table 1 lists the characteristic values associated with those responses. In all cases, the responses show a frequency independent capacitance in the kHz region, with a dispersion in the capacitance and loss at lower frequencies. In terms of the electrical behaviour of the samples, the increase in dielectric loss with decreasing frequency is typical of materials which are showing a small conductance which will only be observed at low frequencies due to the value of G/ω being correspondingly high. There are a number of mechanisms by which this conductance may arise. Firstly, the sample may exhibit simple d.c. conductivity, indicating free movement of charge through the system, in which case the value of G will be frequency independent. Consequently, G/ω will decrease on lowering the frequency with a gradient of -1 when plotted logarithmically against log frequency. The sample may also exhibit quasi-d.c. conductivity, in which case charge may be considered to move through the system by a series of 'jumps' between sites within the material (Hill and Jonscher, 1983). This type of behaviour is characterised by power law behaviour, i.e., the log/log slopes mentioned above will be greater than -1. Furthermore, the capacitance will also rise with decreasing frequency to give an identical logarithmic slope. The capacitance will also increase with decreasing frequency if a barrier layer is present at the electrode surface. Such layers may arise due to the presence of charges at the electrode surface as a result of either charge injection from the electrodes or an accumulation of charges from the material itself. Furthermore, such layers may arise due to the adsorption of other components of the sample onto the electrode surface such as dissolved polymers (Craig et al., 1994), although such a mechanism is not likely to be of relevance to the present systems. It is therefore possible to distinguish between these various mechanisms by examining the slopes of the capacitance and loss curves when plotted on logarithmic scales against log frequency.

In general, Gelucires with a high HLB (50/13 and 55/18) showed much higher responses (in term of capacitance and conductance) than those with low HLB values. However, examination of the values of capacitance and conductance in Table 1 showed no direct relationship between the dielectric responses and the values of HLB of the samples, despite the fact that both may be considered to be reflections of the polarity of the materials. For example, the values of both capacitance and conductance of Gelucire 55/18 were lower than those of 50/13 in spite of the higher HLB value of the former. Furthermore, the value of conductance of 54/02 (at 10 kHz) was higher than that of 50/02 despite their equal HLB values. A further general observation is that, where differences were observed between the responses of samples cooled using different rates, the values

Table 1

Characteristic values of capacitance, conductance and log/log slope of dielectric loss associated with the dielectric response of Gelucires (A, slow cooled; B, fast cooled)

Sample	C (F)($\times 10^{-12}$) at 10 kHz	C (F)($\times 10^{-12}$) at 0.1 Hz	G (Mho)($\times 10^{-9}$) at 10 kHz	Slope of log G/ω against log $\omega < 1$ Hz [a]
A43/01	0.72	2.24	0.63	—
B43/01	0.79	1.45	0.63	—
A54/02	0.87	10.5	4.66	0.92
B54/02	0.96	2.69	2.50	—
A50/02	0.85	4.07	0.97	0.98
B50/02	0.91	3.02	1.20	0.99
A50/13	1.35	408	29.42	0.90
B50/13	1.48	40.7	30.11	0.91
A55/18	0.98	60.3	3.70	0.96
B55/18	0.96	40.7	3.38	0.96

[a] Slope calculated (where possible) from linear portion of log G/ω against log ω graph at lowest frequencies studied.

of capacitance and loss were generally higher in the slowly cooled samples than in the fast cooled samples.

Gelucire 43/01 is a mixture of triglycerides while Gelucire 54/02 contains a mixture of di-and monoglycerides. The responses of Gelucires 43/01 and 54/02 are shown in Figs. 1 and 2, respectively, and characteristic parameters are given in Table 1. Gelucire 43/01 shows a frequency-independent capacitance at high frequencies, with a dispersion in both the capacitance and loss seen at lower frequencies. A clear difference was seen between samples prepared by slow and fast cooling at low frequencies, with the former showing a higher dielectric loss. These differences were even more marked for Gelucire 54/02 samples. Furthermore, the low frequency loss slope of the slow cooled sample indicated that this sample was exhibiting near-d.c. conductivity, as indicated by the slope of the low frequency loss curve which was close to − 1. The low frequency dispersion in the capacitance indicates the presence of an electrode layer, although it is not possible to ascertain the nature of this layer from the data given here.

It is possible to calculate the dielectric constants of the two materials at 10^4Hz (i.e., in the region where the capacitance is frequency-independent) using Eq. 3. The values for Gelucire 50/02 are approx. 2.8 and 3.1 for the slow and ambient samples, respectively, while for Gelucire 54/02 the values are 3.4 and 3.7. The higher values seen for the Gelucire 54/02 may reflect the lower substitution of the glycerides present in this sample.

Figs. 3 and 4 show the dielectric responses of Gelucires 50/02 and 50/13, respectively, with characteristic parameters being given in Table 1. Both materials are mixtures of glycerides and PEG esters, albeit in different proportions. The spectra indicates that Gelucire 50/02 also shows d.c. conductivity, the response of this sample showing a much smaller dependence on cooling rate. Gelucire 50/13, however, again showed a

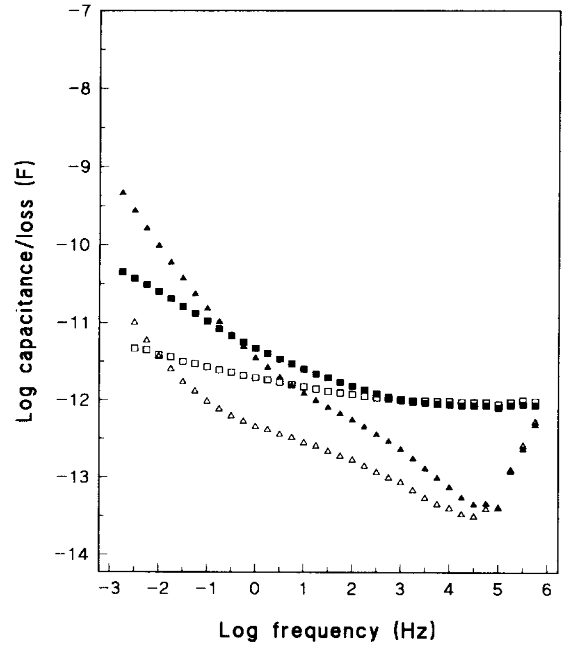

Fig. 2. Dielectric response of Gelucire 54/02. (□, △) Capacitance and loss of fast cooled sample; (■, ▲) capacitance and loss of slow cooled sample.

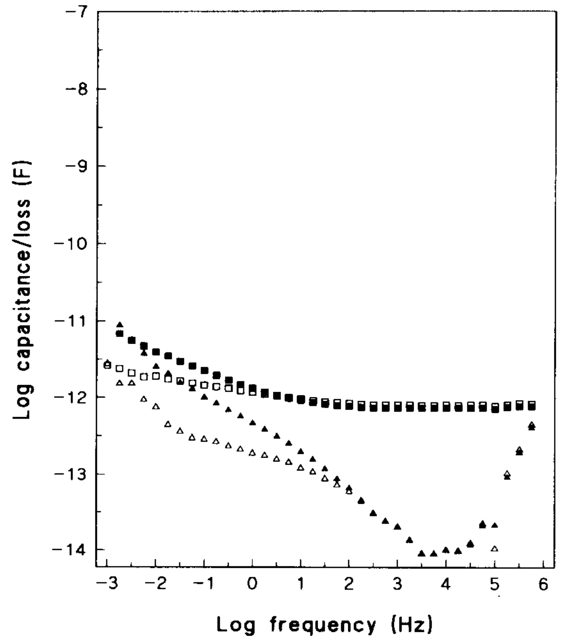

Fig. 1. Dielectric response of Gelucire 43/01. (□, △) Capacitance and loss of fast cooled sample; (■, ▲) capacitance and loss of slow cooled sample.

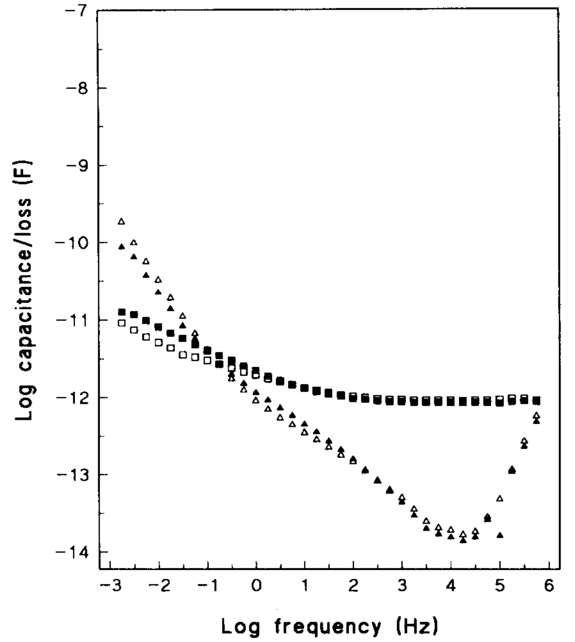

Fig. 3. Dielectric response of Gelucire 50/02. (□, △) Capacitance and loss of fast cooled sample; (■, ▲) capacitance and loss of slow cooled sample.

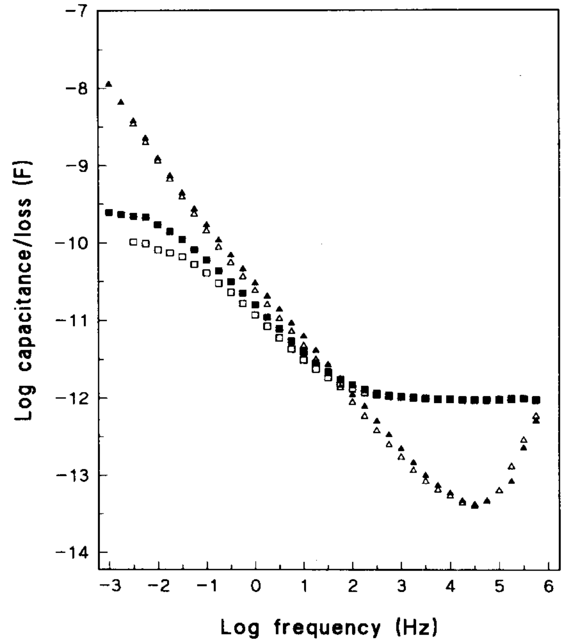

Fig. 5. Dielectric response of Gelucire 55/18. (□, △) Capacitance and loss of fast cooled sample; (■, ▲) capacitance and loss of slow cooled sample.

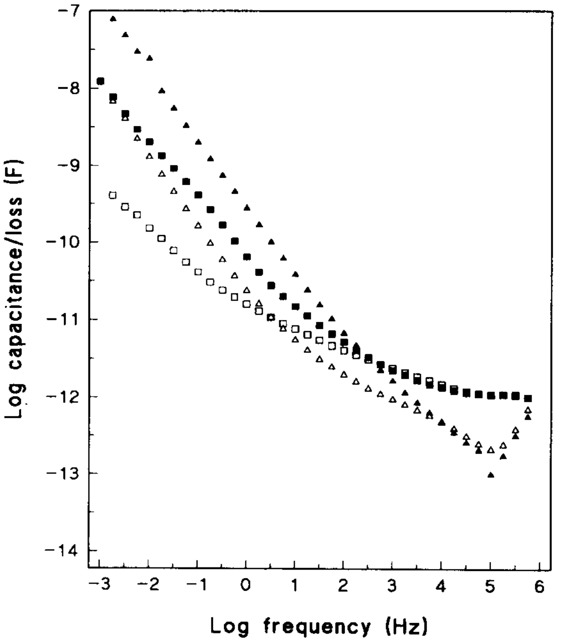

Fig. 4. Dielectric response of Gelucire 50/13. (□, △) Capacitance and loss of fast cooled sample; (■, ▲) capacitance and loss of slow cooled sample.

considerably greater low frequency response when the samples had been previously slow cooled.

Finally, the response of Gelucire 55/18 is shown in Fig. 5. This material is composed of polyoxyethylene stearate and contains no glycerides. The dielectric spectra are similar to those of polyethylene glycols (e.g., Craig et al., 1993), although the values of capacitance and conductance were about an order of magnitude lower in Gelucire 55/18 than in PEG 6000. Chatham (1985) has suggested that the low frequency response of PEG 4000 may be associated with the hydroxyl end groups which are rejected from the crystalline lamellae. Gelucire 55/18 possesses bulky fatty acids end groups and a limited number of hydroxyl end groups (in PEG monostearate), hence the lower values of conductance and capacitance compared to PEGs may be related to this structural feature. Like Gelucire 50/02, the response of this samples showed a relatively small dependence on previous cooling rate.

4. Discussion

This study has involved the measurement of a range of Gelucire samples using low frequency dielectric spectroscopy with a view to examining the relationship between the dielectric response and structure. There are essentially two considerations involved in the interpretation of the results. Firstly, it is necessary to consider the spectra in terms of dielectric processes. The second consideration is the relationship between the dielectric behaviour of the sample and the physical structure of that material. This is an area which has not been extensively explored but has clear implications for the development of dielectric analysis as an analytical tool within the pharmaceutical field.

In order to interpret the dielectric response in term of the sample structure, it is necessary to consider both the differences between the Gelucire samples and also the differences between slow and fast cooled materials. While these materials are in themselves complex, there are a limited number of explanations for the observed differences and these will be described in detail below.

Clearly, changes in the gross chemical nature of the Gelucires may be expected to result in changes in the dielectric response. While the various samples did indeed show markedly different responses, there was no clear correlation between the magnitude of the response and the composition. While in general the more hydrophillic samples showed a higher response than the more hydrophobic bases, Gelucire 50/13 showed larger values of capacitance and loss than did the more hydrophillic Gelucire 55/18. Furthermore, differences were seen between slow and fast cooled materials, even though the chemical composition would have remained identical (given the proviso of chemical stability discussed below). It may therefore be concluded that the chemical composition is not in itself the sole determining factor which governs the dielectric response.

The presence of impurities may have a significant effect on the dielectric spectra, as in many materials the impurities may be the only molecules with sufficient mobility to elicit a measurable dielectric response (e.g., Chatham, 1985). The differences between slow and fast cooled samples would suggest that trace metal impurities are not the dominant factor, as such levels would not be expected to be dependent on cooling conditions of the same material. Similarly, while trace water may be of importance, one would expect the slow and fast cooled samples to show much greater differences for the more hydrophillic bases than for those containing pure glycerides, as these materials are considerably more hygroscopic and may therefore be expected to show greater changes in water levels following changes in processing conditions. In fact, no such trend was observed. Finally, it is possible that the heating and cooling process caused different levels of oxidation products to be present in the samples. This would certainly explain the consistently higher response seen for slowly cooled samples, as such materials are subjected to heat for longer periods and may therefore be more likely to undergo oxidation. However, the lack of any clear correlation between chemical composition and sensitivity to cooling conditions casts some doubt on this explanation, as one would expect certain components to be more susceptible to oxidation that others, hence a relationship could reasonably be expected. Furthermore, the glycerides used in Gelucires are hydrogenated in order to minimise the risk of oxidation, hence it is unlikely that extensive oxidation would have taken place given the comparatively mild conditions used in these experiments. Therefore, while the presence of impurities may well be an important factor in determining the response of the different Gelucires, it is less likely to account for changes in response seen using different cooling conditions.

In addition to changes in the chemical composition of the samples, clearly the physical structure must also be considered. Differences in crystallite size (at least on a microscopic scale) is unlikely to be an important factor when the data presented here is considered in conjunction with microscopic data presented in previous studies. For example, Gelucire 50/02 showed considerable differences in crystallite sizes depending on cooling conditions (Sutananta, 1993). However, very little change was observed in the dielectric response. Similarly, previous studies (Sutananta et al., 1994a) indicated that many Gelucires are partially liquid at room temperature, although examination of the level of liquid material from the DSC data does not show a correlation between this factor and the dielectric response. There is also no obvious correlation between the heat of fusion and the dielectric response, other than the observation that slow cooled samples tend to have both a higher heat of fusion and dielectric response. However, the sensitivity of some Gelucires to cooling conditions seen in the dielectric studies are not mirrored by heat of fusion results.

The presence of different polymorphs in the slow and fast cooled samples may be of relevance to the dielectric response. Previous studies (Sutananta et al., 1994a,b) have suggested that the issue of polymorphism is not applicable to the behaviour of Gelucires, as the number of components within these materials is so large that crystals of pure materials are unlikely to be seen. A more pertinent consideration is the segregation of the various components into different regions within the sample. There does appear to be a correlation between the dielectric response and the tendency of these materials to segregate into distinct melting regions, as indicated by the presence of sharp peaks on the DSC traces. For example, slow cooled Gelucire 43/01 showed a greater tendency to exhibit sharp peaks than did the fast cooled material (Sutananta et al., 1994a). This Gelucire also showed a higher response for the slow cooled material. Gelucire 50/02, however, showed less sensitivity to cooling rate in terms of both the tendency to segregate and the dielectric response, while 54/02 showed marked differences on both counts, as did Gelucire 50/13. Similarly, smaller changes were observed for Gelucire 55/18 using both criteria.

There is therefore evidence that the difference between slow and fast cooled samples is a function of the structural homogeneity of the samples. If segregation has occurred (indicated by separate DSC peaks), then it is reasonable to assume that interfaces will exist between these regions which, for regions outlined earlier, will give rise to a dielectric response. If, however, the DSC peaks are broad and featureless, the material will not have separated into distinct regions. It is possible that the interfaces present in slow cooled samples between the different melting regions will not be present, hence the dielectric response will be lower.

5. Conclusions

The study has examined the factors which influence the low frequency dielectric response of Gelucires, with a view to developing the use of this technique as a means of characterising pharmaceutical solids. The data indicate that not only may changes in the chemical nature of the Gelucires be detected, but also the physical structure, notably the tendency of the samples to segregate into distinct microcrystalline regions. This may be of relevance to previous observations (Craig et al., 1991) which indicated that the technique is capable of detecting interbatch variation in lactose samples. The study has therefore demonstrated that the technique has potential as a solid-state analytical tool within the pharmaceutical sciences.

References

Chapman, D., The polymorphism of glycerides. *Chem. Rev.*, 62 (1962) 433–456

Chatham, S.M., Characterisation of molten filled hard gelatin capsules. Ph.D Thesis, Chelsea Department of Pharmacy, University of London (1985).

Craig, D.Q.M., *Pharmaceutical Application of Dielectric Spectroscopy*, Taylor & Francis, London, 1995b, in press.

Craig, D.Q.M., The use of glycerides as controlled release matrices. In Karsa, D.R. and Stephenson, R.A. (Eds), *Excipients and Delivery Systems for Pharmaceutical Formulations*, Royal Society of Chemistry, London, 1995a, pp. 148–173

Craig, D.Q.M., Davies, C.F., Boyd, J.C. and Hakes,L.B., Characterisation of variation between batches of Fast-Flo lactose using low frequency dielectric spectroscopy. *J. Pharm. Pharmacol.*, 43 (1991) 444–445

Craig, D.Q.M., Hill, R.M. and Newton, J.M., An investigation into the low frequency dielectric response of polyethylene glycols. *J. Mater. Sci.*, 28 (1993) 405–410

Craig, D.Q.M., Tamburic, S., Buckton, G. and Newton, J.M., An investigation into the structure of Carbopol 934 gels using dielectric spectroscopy and oscillatory rheometry. *J. Controlled Release*, 30 (1994) 213–223

Crowe, R.W. and Smyth, C.P., Molecular rotation and proton transfer in the solid form of 1-monopalmitin and 1-monostearin. *J. Am. Chem. Soc.*, 72 (1950a) 4427–4432

Crowe, R.W. and Smyth, C.P., The dielectric and molecular behaviour of 1,3-dipalmitin, 1,3-distearin, tripalmitin, tristearin and teradecyl palmitate. *J. Am. Chem. Soc.*, 72 (1950b) 5281–5287

Crowe, R.W. and Smyth, C.P., The low-frequency dielectric properties of some symmetrical mixed triglycerides in the solid state. *J. Am. Chem. Soc.*, 73 (1951) 2040–2045

Dissado, L.A. and Hill, R.M., Non-exponential decay in dielectrics and dynamics of correlated systems. *Nature*, 79 (1979) 685–689

Hill, R.M. and Jonscher, A.K., The dielectric behaviour of condensed materials and its many-body interpretation. *Contemp. Phys.*, 24 (1983) 75–110

Parkash, S. and Blanshard, J.M.V., Dielectric loss as a parameter for the study of polymorphism in trierucin. *J. Food Technol.*, 9 (1974) 297–299.

Sutananta, W., The physical characterisation of complex glyceride mixes. Ph.D Thesis, School of Pharmacy, University of London (1993).

Sutananta, W., Craig, D.Q.M. and Newton, J.M., An evaluation of the mechanisms of drug release from glyceride bases *J. Pharm. Pharmacol.*, 47 (1995a) 182–187.

Sutananta, W., Craig, D.Q.M. and Newton, J.M., An investigation into the effect of preparation conditions on the structure and mechanical properties of pharmaceutical glycerides *Int. J. Pharm.*, 110 (1994a) 75–91

Sutananta, W., Craig, D.Q.M. and Newton, J.M., An investigation into the effects of preparation conditions and storage on the rate of drug release from pharmaceutical glycerides bases *J. Pharm. Pharmacol.*, 47 (1995b) 355–359.

Sutananta, W., Craig, D.Q.M. and Newton, J.M., The effects of ageing on the thermal behaviour and mechanical properties of pharmaceutical glycerides *Int. J. Pharm.*, 111 (1994b) 51–62