An investigation into the thermal behaviour of an amorphous drug using low frequency dielectric spectroscopy and modulated temperature differential scanning calorimetry

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Abstract

The objective of the study was to investigate the use of low frequency dielectric spectroscopy as a means of characterizing the thermal transitions of an amorphous drug substance, indometacin, with particular emphasis on modelling the response using the Dissado–Hill function.

The low frequency dielectric behaviour of indometacin was measured over a temperature range of 10–160°C and a frequency range of 10^{-3}–10^6 Hz. Modulated temperature differential scanning calorimetry (MTDSC) studies were also performed on equivalent samples, showing a glass transition, recrystallization and melting. Isothermal low frequency dielectric spectra of the sample at temperatures below recrystallization showed the dynamic dielectric relaxation associated with the amorphous phase, while changes in the real and imaginary permittivities were observed that were associated with recrystallization and subsequent melting. A small discontinuity was observed immediately above the recrystallization process in the MTDSC and dielectric data, suggested to correspond to a solid state transformation. The use of the Dissado–Hill function as a means of modelling the dielectric behaviour has also been described.

The study suggests that low frequency dielectric spectroscopy, used in conjunction with MTDSC and Dissado–Hill modelling, may be a useful tool for the characterization of amorphous and crystalline drugs.

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Introduction

The characterization of amorphous pharmaceutical materials has been the subject of considerable study in recent years (Hancock et al 1995; Hancock & Zografi 1997; Craig et al 1999). In particular, the necessity of effectively assessing the glass transitional behaviour of such systems is well recognized. Recently, however, emphasis has been placed on understanding the relaxation behaviour of amorphous drug systems above and below T_g to aid predictability of the behaviour on storage (Hancock et al 1995; Shamblin et al 1999; Craig et al 2000). This increased sophistication of the knowledge requirements associated with the glassy state has highlighted the necessity of considering a wider range of characterization techniques than has previously been the case. One approach that has received increasing attention within the pharmaceutical field is dielectric analysis (Craig 1995). This

technique involves the application of an electric field to a sample and the measurement of the response in the frequency and/or temperature domains. The approach is well established within the thermal analysis and polymer science fields as an important technique for the investigation of the dynamics of relaxation processes involving large scale or local molecular motions. Analysis in the frequency domain allows characterization of relaxation behaviour of samples without the necessity of that material undergoing a specific thermal event and also affords the possibility of modelling the response in terms of an equivalent circuit (Dissado et al 1987; Goggin et al 1998; He & Craig 1998a). Similarly, analysis in the temperature domain allows identification of a range of thermal events such as glass transitions (McCrum et al 1967; Hedvig 1977). The method has been used for the study of a range of pharmaceutical systems including freeze-dried products (Yoshioka et al 1999), liquid crystalline materials (He & Craig 1998b) and amorphous drugs (Andronis & Zografi 1998; Barker et al 2000).

The technique has been shown to be of particular use for the assessment of the relaxation behaviour via isothermal frequency sweeps, whereby the loss peak corresponding to the dipolar relaxation may be measured, from which the relaxation time may be ascertained. In this investigation, we have examined two further aspects of the use of the dielectric technique (or more specifically the low frequency dielectric technique, which covers the kHz to mHz range). Firstly, we have described the use of the technique to study a model amorphous drug (indometacin) over a wide temperature range to include recrystallization and melting processes. Secondly, we have described the use of the Dissado–Hill function as a means of modelling the response. Dielectric behaviour almost invariably deviates from the ideal Debye response, hence a number of modifications have been described to account for the ideality including the Cole-Cole, Davidson and Cole and the Havriliak and Negami functions (Hill 1981). In recent years, however, interest has been generated in the use of the Dissado–Hill function (Dissado & Hill 1979) whereby the behaviour of the material is considered in terms of a cluster model (see later for more details), thereby facilitating fitting of experimental data on a non-empirical basis. This function has been effectively used for a number of polymeric, colloidal and semi-conductor systems (Shablakh et al 1982; Hill & Jonscher 1983; Ramdeen et al 1984) but has not yet been extensively applied to pharmaceuticals. We have reported on the use of this fitting function and have discussed the putative interpretation of the experimental data in terms of the cluster model.

Materials and Methods

Crystalline indometacin was obtained from Fluka and used as received. Amorphous indometacin samples were prepared by cooling from the melt. The crystalline indometacin was placed in the lower part of a dielectric cell designed for liquid and powder samples (Novocontrol GmbH), and heated to the melt at approximately 160°C. The upper electrode of the dielectric cell was inserted to form a uniform sample (diameter 18 mm, thickness 1.5 mm) and to prevent absorption of moisture from the air. The cell was then removed from the heater and cooled to room temperature over a 3-h period.

Dielectric measurements were carried out using a BDC-N broad band dielectric converter (Novocontrol GmbH) and a SI 1255 frequency response analyser (Solatron-Schlumberger) linked to a Quatro temperature control system (Novocontrol GmbH). This technique involves the application of an oscillating electrical field to a sample and the subsequent measurement of the real and imaginary components of the response over a range of frequencies (ω). This response may be expressed in terms of the complex permittivity $\epsilon^*(\omega)$, where

$$\epsilon^*(\omega) = \epsilon'(\omega) - i\epsilon''(\omega) \tag{1}$$

with ϵ' and ϵ'' being the real and imaginary components at frequency ω and i being the square root of -1. These components may be measured in terms of the extrinsic parameters $C(\omega)$ and $G(\omega)/\omega$, where $C(\omega)$ is the capacitance and $G(\omega)/\omega$ is the dielectric loss, $G(\omega)$ being the conductance (representing the sum of the a.c. and d.c. contributions), from which the real and imaginary permittivities may be calculated via

$$\epsilon'(\omega) = \frac{C(\omega).d}{\epsilon_0 A} \tag{2}$$

$$\epsilon''(\omega) = \frac{G(\omega)}{\omega}.\frac{d}{\epsilon_0 A} \tag{3}$$

where ϵ_0 is the permittivity of free space, and d and A are the interelectrode distance and electrode area, respectively.

The dielectric spectra as a function of frequency and temperature were obtained by measuring isothermal responses over a frequency range of 10^{-3}–10^6 Hz at selected temperatures with 4°C increments over a range of 10–160°C (precision 0.1°C), using a heating rate of 2°C min^{-1}. Each spectrum measurement took approximately 45 min. The real and imaginary components of
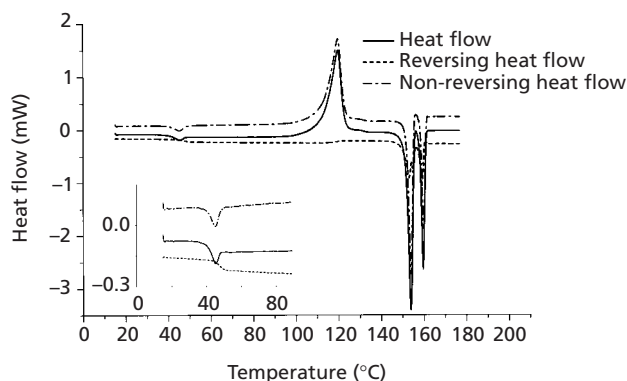
Figure 1 Modulated temperature DSC response of amorphous indometacin, with details of the glass transition region shown inset.

the measured data in the frequency domain were fitted simultaneously by employing a Dissado–Hill model and using the Winfit 2.6 program supplied by Novocontrol GmbH.

Modulated temperature DSC (MTDSC) studies were conducted on the amorphous material over a temperature range of 20–180°C. A TA Instruments 2920 Modulated DSC with a sample size of approximately 4 mg and TA Instruments aluminum DSC pans (hermetically sealed) were used, the modulation period was 30 s, and an amplitude of ± 0.16°C with a heating rate of 2°C min^{-1} was applied. Samples were prepared by melting the crystal indometacin at 160°C in a DSC pan and cooling at room temperature over a 3-h period. Calibration was performed with indium, cyclohexane and tin standards, using the same underlying heating rate and the same pan type as in the experiments. All dielectric and MTDSC studies were repeated four times.

Figure 2 Three-dimensional dielectric spectra of amorphous indometacin as a function of frequency and temperature. A. Real permittivity. B. Imaginary permittivity.

Results

Figure 1 shows the MTDSC scan for the indometacin glass over the temperature range of 20–180°C. The total heat flow shows a discontinuity in the baseline at approximately 47°C that was seen in the reversing and non-reversing signals to correspond to a glass transition and accompanying relaxation endotherm. A recrystallization exotherm was seen in the total and non-reversing signals with an extrapolated onset of 113.1°C, with a corresponding decrease in heat capacity noted in the reversing heat flow signal. A double melting peak at 154°C and 160°C was then observed that may be
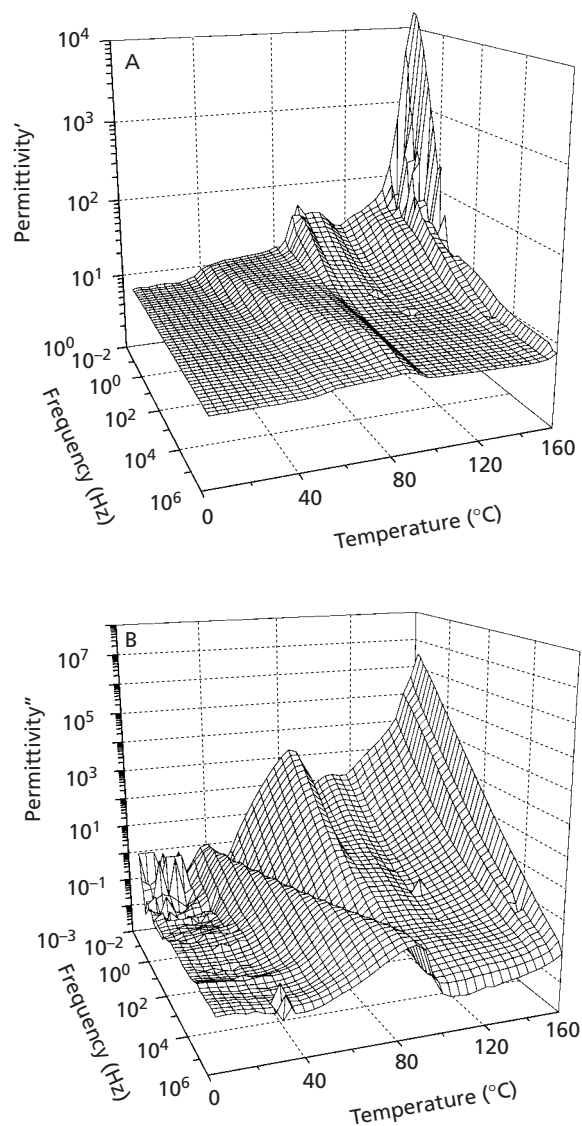
ascribed to the melting of the α and γ polymorphic forms of indometacin (Kistenmacher & Marsh 1972; Yoshioka et al 1994). While the presence of these two melting peaks was seen for each repeat measurement the reproducibility of their relative sizes was found to be poor. This had been noted previously for systems that had been recrystallized from the amorphous state during a DSC scan (Bottom 1999) and appears to be a common difficulty associated with such measurements. A small but reproducible discontinuity was also seen in the total and non-reversing signals at approximately 120–130°C, possibly representing a further solid-state process. It
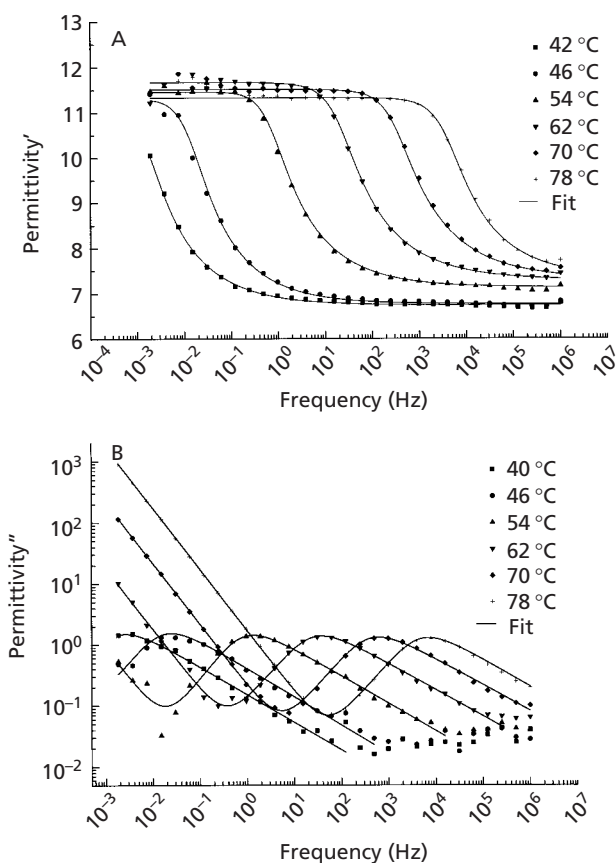
Figure 3 Low frequency dielectric responses of amorphous indometacin. A. Real permittivity. B. Imaginary permittivity.

Figure 4 Low frequency dielectric responses of recrystallized indometacin at 102°C.

should be noted that it was not possible to interpret the reversing heat flow signal during the melting process due to the system not being in steady state (Craig & Royall 1998).

Figure 2 shows the dielectric response for glassy indometacin presented in a three-dimensional graphic as a function of frequency and temperature. In the real and imaginary permittivities, five temperature response patterns were seen. Firstly, at temperatures below 40°C, the dielectric permittivity was almost frequency and temperature independent, although some noise was seen in the imaginary signal, particularly at low frequencies due to the magnitude of the response being close to the limit of sensitivity of the instrument. Secondly, a frequency dependent step increase in the real permittivity and a corresponding frequency-dependent relaxation peak seen in the loss response were seen between approximately 40°C and 90°C. Thirdly, a low frequency maximum was seen in the real and loss components over a temperature range of approximately 92–118°C. A further small low frequency maximum was shown at
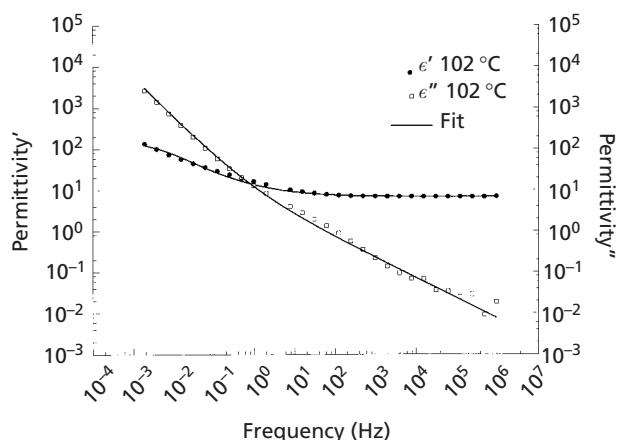
approximately 120–140°C, and finally a substantial rise in both components appeared at temperatures higher than 150°C.

Figure 3 shows the frequency dependent behaviour over a more limited range of temperatures (42–78°C) to allow a clear visualization of the relaxation peak and corresponding increase in permittivity for the glassy system. Figure 4 is the spectrum at 102°C, showing a typical solid response at high temperatures.

As mentioned previously, one of the possibilities afforded by frequency domain dielectric studies is the modelling of the spectra, although there is continued debate regarding the choice of correction for non-Debye behaviour. The interpretation based on the Dissado–Hill theory (Dissado & Hill 1979) has attracted interest due to the applicability of the approach to a range of systems in the liquid and solid phases (irrespective of the obvious presence of relaxation peaks) and the well defined theoretical background associated with the mathematical treatment of the data.

The approach developed as a result of the Dissado–Hill theory is based on the premise that the deviations from Debye behaviour are due to many-body interactions and that such interactions may be mathematically described by the correlation coefficients (m and n) in the spectral shape function. This function describes the extent of decoupling of the relaxing dipolar species from the surrounding environment and is defined as:

$$\epsilon^*(\omega) = \epsilon' - i\epsilon''$$

$$= \epsilon_\infty - i\frac{\sigma_0}{\epsilon_0\omega} + \frac{\Delta\epsilon}{(1+i\omega\tau)^{n-1}}\frac{1}{F_{01}^2}F_1$$

$$\left(1-n, 1-m; 2-n; \frac{1}{1+\omega\tau}\right) \tag{4}$$

where σ_0 is the d.c. conductance, $\Delta\epsilon = \epsilon_1 - \epsilon_\infty$ is the dielectric strength, ϵ_1 and ϵ_∞ are the low and high frequency limits of the dielectric constant, respectively, $_2F_1$ is the Gaussian hypergeometric function given by

$$_2F_1(a,b\,;c\,;z) = \sum_{n=0}^{\infty}\frac{(a)_n(b)_n}{(c)_n}\frac{z^n}{n!} \qquad (5)$$

with:

$$(a)_n = a(a+1)(a+2)\ldots(a+n-2)(a+n-1) \qquad (6)$$

F_{01} is the normalizing parameter described as:

$$F_{01}(n,m) = \frac{\Gamma(2-n)\Gamma(m)}{\Gamma(1+m-n)} \qquad (7)$$

where Γ is the Gamma function. The indices n and m have been determined as the correlation coefficients for specific intra-cluster and inter-cluster relaxation mechanisms, respectively, and lie between 0 and 1. In essence, the parameter n indicates the extent to which neighbouring dipoles interact within a cluster i.e. this component reflects short-range correlations. The parameter m, however, refers to the equivalence of neighbouring clusters, with a value of $m = 0$ indicating perfect equivalence while $m = 1$ indicates inhomogeneity between clusters. On this basis, m can be considered to represent long-range interactions between clusters of dipoles.

The frequency responses of the indometacin sample over the temperature range T_g to T_m were fitted using the Dissado–Hill function. Typical fitting plots for the frequency responses in the amorphous and recrystallized phases are shown as the solid lines in Figures 3 and 4, respectively; the mean square deviation of the fitting was less than 5×10^{-2}. The fitted relaxation times τ, d.c. conductance σ_0 and indices n and m are plotted as a function of temperature in Figure 5.

Discussion

The first objective of the study was to examine the dielectric response of amorphous indometacin over a wide temperature range, with a view to developing the use of low frequency dielectric analysis as a means of characterizing pharmaceuticals. The second was to examine the use of the Dissado–Hill function as a means of modelling the dielectric data.

To evaluate the ability of the dielectric approach to characterize the phases and thermal transitions associated with amorphous indometacin it is helpful to con-
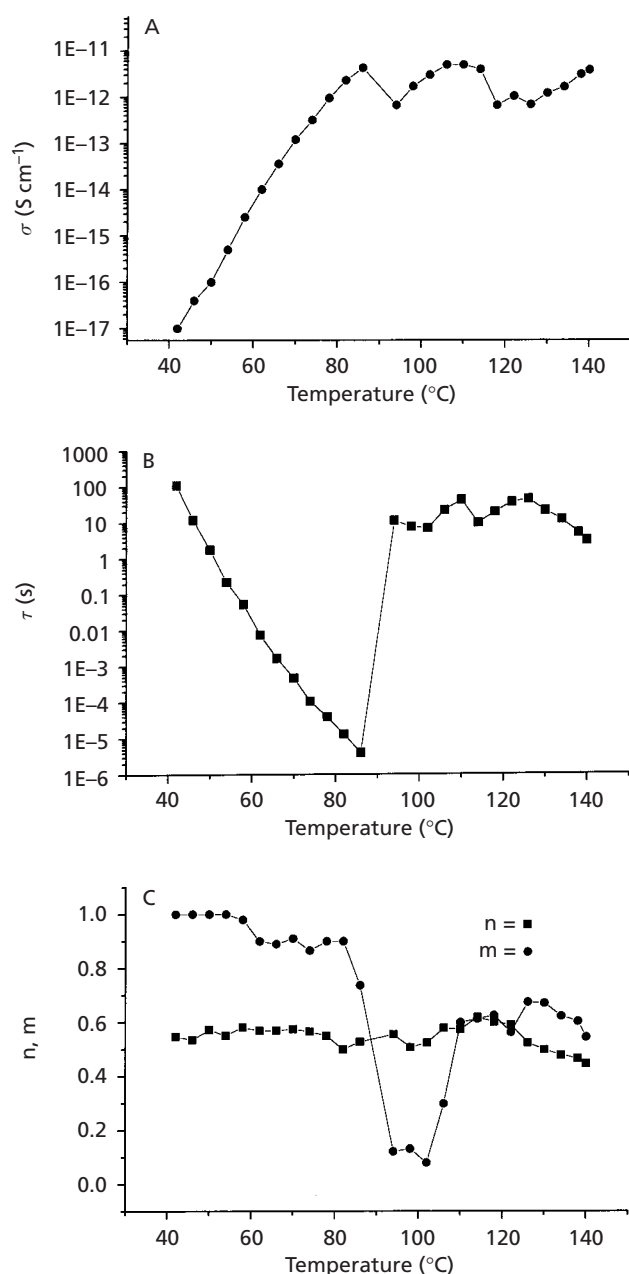

Figure 5 Plots of fitted parameters for the dielectric responses over a temperature range of 40–140°C. A. d.c. conductance. B. Relaxation time. C. Correlative parameters.

sider the interpretation of the low frequency dielectric results in the light of the data from the MTDSC studies. Clearly, the precise temperatures and energies associated with the various thermal events will vary between the two methods due to differences in sample size, sample preparation and thermal history. Nevertheless, comparison between the data sets is valid from the viewpoint

of identifying the physical basis of the observed dielectric features.

At temperatures below 40°C, the sample was in the glassy ($< T_g$) state. The real component of the permittivity was found to be almost frequency independent (value approximately 6.5) over the range studied, while the value of the imaginary component was low. This reflects a rigid structure in which the relaxation of molecules was very slow, hence any low temperature relaxation process lies outside the accessible experiment range and could not be detected. At approximately 42°C and above an incremental increase and a loss peak was seen in the real and imaginary components, respectively (Figures 2 and 3). This behaviour corresponded to the relaxation process associated with the glass, as previously discussed by Andronis & Zografi (1998). The relaxation peak was broad and non-symmetrical, corresponding to non-Debye behaviour as is expected for relaxation in a condensed system. The frequency location of the ϵ'' peak maximum was $\omega_{max} = 1/\tau$, thus the mean relaxation time τ of the dipole molecules at a given temperature could be determined. The wide frequency range available using this technique is an advantage, as measurement in the sub-Hz range allows assessment of correspondingly long relaxation times. A concomitant rise in ϵ'' was seen at lower frequencies as the temperature was raised due to conductance effects. This may be understood with reference to equation 3, with the term G referring to all conductance processes taking place at any frequency ω. The imaginary permittivity was directly proportional to the dielectric loss G/ω, hence small conductances will only be seen in ϵ'' at low frequencies. Furthermore, the slope of the loss process was approximately -1, indicating a frequency independent value of G that in turn indicated d.c. conductance.

Comparison with the MTDSC data indicated that the low frequency maximum seen at approximately 90°C corresponded to the recrystallization process. However, caution is required in the detailed assignation of this response as the peaks in the DSC and dielectric data have different origins. The DSC data was obtained by scanning through the temperature domain and reflects heat flow as a function of temperature. The dielectric response shown in Figure 2, however, was obtained via a series of isothermal scans through the frequency domain. Consequently, the sub-Hz increase in imaginary permittivity with temperature seen in Figure 2B between approximately 45 and 90°C does not reflect the onset of crystallization but instead reflects an increase in conductance at temperatures above that corresponding to the relaxation peak. In fact, the crystallization process

was reflected by a decrease in ϵ'' immediately following the maximum as the molecular mobility, and hence conductance, was lowered. It was also interesting to note that a further maximum was seen in the low frequency dielectric response at approximately 100–120°C that appeared to correspond to the small discontinuity seen in the MTDSC data. While further studies are required to identify the origin of this response, it is interesting to speculate that it may correspond to a solid-state reaction, possibly between different polymorphic forms. Irrespective of the underlying mechanism it is noted that the event was clearly visible in the low frequency response.

At higher temperatures the dielectric peak corresponding to the dynamic glass transition was no longer observed, as expected for a system that has undergone crystallization (Figure 4). The response consisted of dispersive relaxation processes without significant loss peaks and showed relatively weak temperature dependence (Figure 2A and B). These features are typical of a solid system with structurally determined dielectric properties over this frequency range. The marked increase in permittivity at low frequencies and temperatures higher than 150°C reflected the behaviour of the molten indometacin, with the spectra showing typical liquid responses (data not shown).

A general observation to arise from Figure 2 in particular was that the various transitions often appeared to be more easily observed at lower frequencies, adding weight to the assertion that examination of the sub-Hz frequency range may yield highly useful structural information. First-order processes such as melting or crystallization are frequency independent hence, intuitively, substantial frequency sensitivity would not be expected to be seen. However, when measuring the dielectric response of these systems, it must be considered that multiple dielectric processes may be observed depending on the frequency window as the sensitivity of the dielectric response to such changes may itself vary across the spectrum. In particular, d.c. conductance processes may dominate in the mHz region for solid samples, while at higher frequencies the response may be dominated by dipolar relaxation processes. The observations presented here suggest that the former is particularly sensitive to melting and crystallization, leading to greater sensitivity in the sub-Hz region to such responses.

The information obtained from the fitting may be discussed in terms of the putative mechanisms associated with the fitted parameters. The values of σ_0 (Figure 5A) increased from approximately 10^{-17} to 10^{-11} s cm^{-1} over the temperatures between the glass transition and

the recrystallization, indicating a rapid increase of the d.c. conductance of the system as the temperature of the amorphous phase was increased. At the temperatures corresponding to the events associated with recrystallization and putative solid-state transformation (94°C and 118°C), σ_0 decreased by approximately one order of magnitude. The decrease following recrystallization has already been discussed and reflects the higher impedance of the system following solidification. The decrease following the higher temperature response is less easily explained and requires further investigation.

In the dynamic glass transition range of 40–90°C, the relaxation time τ decreased rapidly from 100 to 10^{-6} s (Figure 5B). The temperature dependence was found to obey the Vogel–Tamman–Fulcker (VTF) relationship, given by:

$$\tau = \tau_0 \exp[DT_0/(T - T_0)] \tag{8}$$

where τ_0 is the relaxation time at reference temperature T_0 and D is a material parameter related to the fragility of the sample. The values of the fitted parameters are $\tau_0 = 1.08 \times 10^{-14}$ s, $D = 7.29$ and $T_0 = 263.7$K. These data are in reasonable agreement with those published by Andronis & Zografi (1998). However, the availability of low frequency measurements allowed the fitting to take place over a greater temperature range, thus availing more data for the analysis, hence over and above the analysis described below the equipment does have significant advantages over many alternative models for the study of relaxation behaviour. At the onset temperature of crystallization (approximately 94°C), the relaxation time of the system increased sharply from 10^{-6} s to approximately 10 s as a result of the transformation from the amorphous to the crystalline phase, with concomitant reduction in molecular mobility. We believe that the ability to assess τ not simply over a wide temperature range but also through the amorphous to crystalline phase change represents a potentially useful development, given the current interest in the relationship between relaxation behaviour and drug stability. Indeed there is a paucity of information regarding the relaxation time of crystalline drugs, hence this aspect of the present study may warrant further investigation.

The two correlation indices n and m showed markedly different temperature dependent behaviour. The intra-cluster parameter n showed little change throughout the temperature range studied, with values of approximately 0.55 seen throughout. As this parameter represents short-range correlations, the consistency of the value reflects the similarity of the short-range correlations between the amorphous and glassy state, as is known to be the case for glassy and crystalline systems (Angell

1995). The value of m reflects long-range homogeneity and had a value of approximately 1 for the amorphous state, as would be expected. At temperatures corresponding to the recrystallization process, however, the value decreased to approximately 0.2, almost certainly reflecting the formation of crystallites within the amorphous matrix, thereby reducing the homogeneity of the system. At temperatures above approximately 110°C, the value of m remained constant at approximately 0.6. It is interesting to speculate that, given the above theoretical basis for m, this value may reflect the distribution of crystallites within the solid sample. This is another issue that has not been widely addressed within the pharmaceutical sciences and may merit further investigation.

Conclusions

The dielectric method was shown to be capable of detecting the major transitions associated with the model drug, particularly in the sub-Hz region, and also allowed direct visualization of the relaxation peak for the amorphous material. In addition, a secondary process was observed using MTDSC and dielectric analysis at temperatures immediately above the recrystallization temperature that has been tentatively attributed to a secondary recrystallization process. The Dissado–Hill function was shown to be capable of fitting the dielectric data in both the amorphous and crystalline phases. The fitting allowed characterization of the conductance, relaxation times and correlation indices, thereby providing a range of potentially useful parameters for the characterization of this material.

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