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Characterization of the structure of drug dispersions in polyethylene glycols using low-frequency dielectric spectroscopy

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Dispersions of a model drug, nortriptyline HCl, in polyethylene glycols 3400, 6000, 10 000 and 20 000 have been studied in both the molten and solid states using low-frequency dielectric spectroscopy. The molten response corresponded to a Maxwell–Wagner system, with a high-frequency conductance in series with a low-frequency barrier-layer capacitance. In comparison to the pure polymers, an increase in conductance was seen on addition of the drug to PEGs 6000 and 10 000, while little change was seen on addition to PEGs 3400 and 20 000. On solidifying the dispersions, the spectra showed a quasi-d.c. response which was associated with the distribution of the amorphous fraction within the sample. These studies indicate that the effect of additive inclusion on the structure of polymeric samples may be usefully examined over the low-frequency dielectric region.

1. Introduction

The medical efficacy of all drug substances is dependent upon the drug being administered to the appropriate site in the body at the appropriate rate. As most drugs are given orally (usually as tablets or capsules), the rate at which absorption across the gastro-intestinal tract takes place is of primary importance. However, prior to absorption it is necessary for the drug to dissolve from the dosage form in order to allow partitioning through the gut membrane. As many drugs have very low solubilities in water, dissolution from the dosage form is frequently the rate-limiting step to absorption. It is therefore desirable to develop medicines which allow rapid dissolution of the active substance in the gastro-intestinal tract. One method of achieving this is to incorporate the drug in a solid water-soluble carrier, such as polyethylene glycol (PEG) in the molecular weight range 3400 to 20 000 [1, 2]. For reasons which are not yet fully understood, the dissolution rate of the drug has frequently been reported to be higher from such solid dispersions than from the pure material [3].

The dispersions may be prepared by heating a mixture of the drug and carrier to the fluid state and subsequently cooling to room temperature. It is necessary to characterize the drug–PEG fusions in order to gain a greater understanding of the mechanisms involved in drug release. In the present investigation, the structure of dispersions containing a water-soluble model drug, nortriptyline HCl, in a range of different molecular weight PEG samples will be examined using low-frequency dielectric spectroscopy (LFDS). This technique has been used previously to examine the PEG samples in the absence of drug [4]. Furthermore, the dispersions have been previously characterized using a range of techniques, including differential scanning calorimetry, scanning electron microscopy and solution calorimetry [5], hence a body of data is available for comparison with the results shown here.

2. Experimental procedure

Nortriptyline HCl (Eli Lilly Ltd, Basingstoke), a tricyclic antidepressant, was used as a model drug. Powder mixes containing 10% w/w nortriptyline HCl in PEGs 3400 (CSD), 6000 (CSD), 10 000 (BDH) and 20 000 (BDH) were prepared and placed in glass cells as described previously [4]. The cells used in the present study differed from those used in the prior investigation in that a borosilicate cover slip (22 mm × 22 mm, thickness 0.5 mm) was used between the electrodes instead of a glass slide in order to obtain the superior insulating properties of the alkali-free borosilicate glass. This allowed more sensitive measurement of the samples. In all cases the area of the electrodes exposed to the sample was 0.72 cm^2. Liquid samples were cooled at approximately 20 K h^{-1} and solid samples at 10 K h^{-1}.

A frequency response analyser (FRA) (Solartron, London) was used in conjunction with a measuring box (Chelsea Interface, Chelsea Dielectrics Group, London) to generate a signal of 1 V. The signal was passed through the sample and subsequently analysed by the FRA to allow calculation of the capacitance (C)

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and loss (G/ω). Measurements were made over a temperature range of 373 to 253 K.

Initial measurements of nortriptyline HCl alone gave a response which was indistinguishable from that of the empty cell, probably due to the limited contact area between the electrodes and the drug crystals. Therefore, a compact was prepared (0.25 g, 1 tonne pressure, diameter 0.7 cm, thickness 0.4 cm) to which adhesive copper tape electrodes were attached (area 0.24 cm^2). This preparation method was found to yield a measurable response for the drug.

3. Results and discussion

3.1. Nortriptyline hydrochloride

The spectra of the solid nortriptyline HCl samples are shown in Fig. 1 over a temperature range of 373 to 313 K. The results have been normalized with respect to 373 K. This technique involves shifting the spectra over a range of temperatures in order to produce a master response curve, the datum points corresponding to the shift required to superimpose the spectra [6]. The response appeared to normalize over the temperature range studied with a capacitance corresponding to a dielectric constant of 11.86. The dielectric loss increased with decreasing frequency, with evidence for a loss peak being seen at approximately 10 Hz at 373 K. This is a comparatively low frequency for the observation of loss peaks and reflects the high viscosity of the medium surrounding the dipoles. It is noted that the frequency, rather than the magnitude of the loss peak, altered with temperature. At lower frequencies a further response is seen, although the noise present below 1 Hz precluded more specific interpretation. The activation energy of the datum point shift was found to be 0.254 eV. As the spectra were normalized with respect to the loss peak, the activation energy given corresponds to that of the relaxation process.

3.2. Solid dispersions

3.2.1. The molten response

The dielectric response of the molten dispersions was measured over a temperature range of 373 to 333 K. The maximum temperature to which the samples were heated (373 K) and was considerably lower than the melting point of the drug (approximately 488.3 K); hence the drug particles may be expected to remain largely intact during the temperature cycling, providing that any interactions between the drug and molten polymer are negligible. Previous studies using differential scanning calorimetry have indicated that at approximately 470 K there is a reduction in the melting point of nortriptyline HCl in 10% w/w dispersions [5], although this may have been a result of the heating process rather than an indication of a direct interaction at room temperature.

A representative response of 10% nortriptyline HCl in molten PEG 3400 is shown in Fig. 2. This spectrum was obtained over a wider frequency range than in the previous study [4], thus allowing clearer examination of the lower-frequency process. Examination of the spectrum suggests a Maxwell–Wagner response, with a high-frequency bulk process in series with a low-frequency barrier-layer response, as described previously [4, 7, 8]. A consequence of this approach is that the sum of the low and high-frequency capacitance log–log slopes is expected to equal -2 [7]. In the present case, the total was found to be -2.032, thus supporting the use of this analysis in the study of liquid systems. It is therefore concluded that the spectrum may be interpreted in terms of a bulk response, dominated by a d.c. conductivity process (as shown by the loss slope of -1.001, which is close to the theoretical value of -1), in series with a low-frequency barrier-layer response. The characteristic parameters of the PEG 3400 dispersions at various temperatures are given in Table I.

The magnitude of the molten PEG response is considerably greater than that of the solid nortriptyline HCl; hence the response may be expected to be dominated by that of the polymer. Comparison of the characteristic parameters for the polymer alone [4] and the 10% w/w drug dispersion (Table I) shows that the high-frequency capacitance and conductance remain similar on addition of the drug, taking into account the differences in cell dimensions used in the two studies. However, the slope of the capacitance curve between $\log f = 0.5$ and 1.5 (where f = frequency

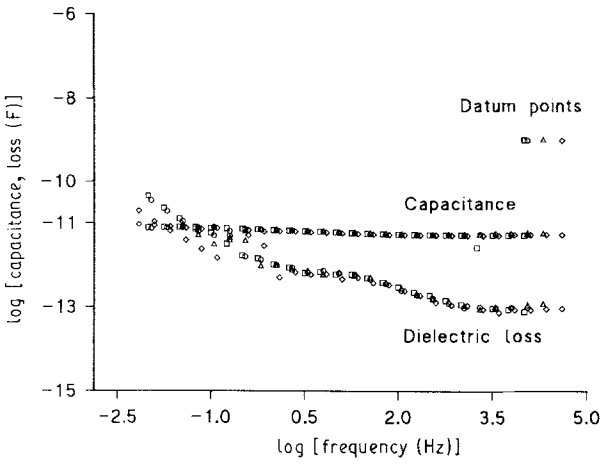

Figure 1 Dielectric response of nortriptyline HCl, normalized to 373 K: (□) 373 K, (○) 363 K, (△) 343 K, (◇) 313 K.

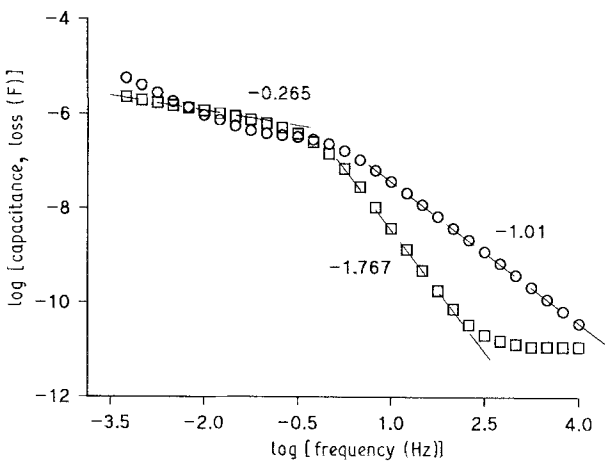

Figure 2 Dielectric response of molten PEG 3400 at 333 K: (□) capacitance, (○) dielectric loss.

TABLE I Characteristic values associated with the dielectric response of 10% nortriptyline HCl in molten PEG 3400

Temperature (K)	C(F)		Conductance (S) at	Slope G/ω,	Slope C,
	$\log f = 4$[a]	$\log f = -1$	$\log f = 4$	$\log f = 2-4$	$\log f = 0.5-1.5$
373	1.215×10^{-11}	1.073×10^{-6}	7.008×10^{-6}	− 0.990	− 1.602
353	1.204×10^{-11}	8.551×10^{-7}	4.343×10^{-6}	− 1.005	− 1.706
343	1.196×10^{-11}	7.537×10^{-7}	3.378×10^{-6}	− 1.003	− 1.743
333	1.187×10^{-11}	3.088×10^{-7}	2.331×10^{-6}	− 1.009	− 1.767

[a] f = frequency (Hz).

TABLE II Characteristic values associated with the dielectric response of 10% nortriptyline HCl in molten PEGs

PEG Mol. wt	C(F)		Conductance (S) at	Slope G/ω,	Slope C,
	$\log f = 4$	$\log f = -1$	$\log f = 4$	$\log f = 2-4$	$\log f = 0.5-1.5$
6000	2.239×10^{-11}	1.854×10^{-6}	1.039×10^{-5}	− 1.000	− 1.807
10 000	2.181×10^{-11}	2.493×10^{-6}	4.085×10^{-5}	− 0.989	− 1.363
20 000	2.061×10^{-11}	2.402×10^{-6}	4.040×10^{-6}	− 1.032	− 1.889

in Hz) is lower for the dispersion sample (− 1.602) than that of − 1.942 for the PEG 3400 alone at 373 K [4]. The slope of the high-frequency capacitance is related to the structure of the barrier layer [7], with a value close to − 2 indicating a blocking layer through which charge may not pass and a higher (less negative) value indicating a "leaky" barrier layer through which charge may move comparatively easily. The presence of the drug is therefore not affecting charge movement through the bulk but is causing the barrier layer to become more permeable to charge movement. This could be due to the drug adsorbing on to the electrodes, thus disrupting the adsorbed PEG layer and facilitating charge movement through the barrier.

The characteristic parameters of the molten response in PEG 6000, 10 000 and 20 000 are shown in Table II. In contrast to the results obtained for PEG 3400, the high-frequency conductance is greater for the dispersions in PEG 6000 and PEG 10 000. These results may indicate some degree of solubility of nortriptyline HCl in the molten PEG, despite the majority of the drug remaining in the solid state [5]. The presence of the drug did not have a marked effect on the response of PEG 20 000. Similarly, PEG 6000, 10 000 and 20 000 showed little change in the capacitance slope, although it is also noted that the low slope value noted for PEG 10 000 alone is also seen for the disperse systems.

The high-frequency conductances were found to be activated over 373 to 333 K for PEGs 3400, 6000 and 10 000, although non-Arrhenius behaviour was seen for PEG 20 000 dispersions. This may be due to partial recrystallization at the lower temperatures studied. In order to allow comparison with the data obtained for the PEGs alone [4], the activation energies have been calculated to include the cell constants used in the two studies and are shown in Table III. There was little difference between the results for the dispersions in PEG 6000 and 10 000 and the PEGs alone, while the result for the PEG 3400 dispersions (which was higher than the other three samples of pure polymer) was lower for the dispersions. The similarity of the activation energies for PEGs 6000 and 10 000 suggests that the presence of the drug may be increasing the conductance by causing a greater number of charges to be present, rather than by altering the mechanism of charge transfer. It has been suggested that the conductance could be due to either a hydrogen-ion hopping mechanism or alternatively due to the presence of impurities [9, 10]. The present results suggest that impurities are responsible for the observed loss behaviour, as it is difficult to visualize how the presence of the drug could increase the extent of hydrogen ion hopping through the sample other than via a catalytic process, which would lower the activation energy. Alternatively, the surface of the solid drug particles could become charged, hence increasing the response of the system via redistribution of charges across the particle surface in the presence of the field [11, 12]. However, this process is associated with a loss peak in the kiloHertz region, which was not observed in the present case.

3.2.2. The solid response

The samples were cooled to the solid state and examined dielectrically over a similar temperature range to that of the polymers alone, although again the samples were studied to lower frequencies than in the previous study [4]. The response of PEG 3400 is given in Fig. 3, the data being normalised to 323 K. The spectra indicates a quasi-d.c. (QDC) process with a crossover frequency at 35.5 Hz (ω_c). This type of response has been discussed in detail by Hill and Pickup [7] and a representative spectrum of an idealized system is shown in Fig. 4. The analysis is based on the assumption of charge movement occurring between clusters of dipoles [13, 14]. The correlation between clusters is indicated by the exponent p, while the homogeneity within single clusters is described by the exponent n, these two regions being seen above and below the critical frequency ω_c. The real and imaginary components are given by

$$C(\omega) \propto G(\omega)/\omega \propto \omega^{-p} \qquad 0 < p < 1 \qquad (1)$$

TABLE III Parameters associated with the Arrhenius relationship between temperature and conductance for 10% dispersions of nortriptyline HCl in molten PEGs

PEG mol. wt	PEG alone		10% dispersion	
	Activation energy (eV)	Correlation coefficient	Activation energy (eV)	Correlation coefficient
3400	0.176	− 0.995	0.126	− 0.997
6000	0.098	− 0.988	0.102	− 0.998
10 000	0.110	− 0.999	0.115	− 1.000
20 000	0.100	− 0.999	–	–

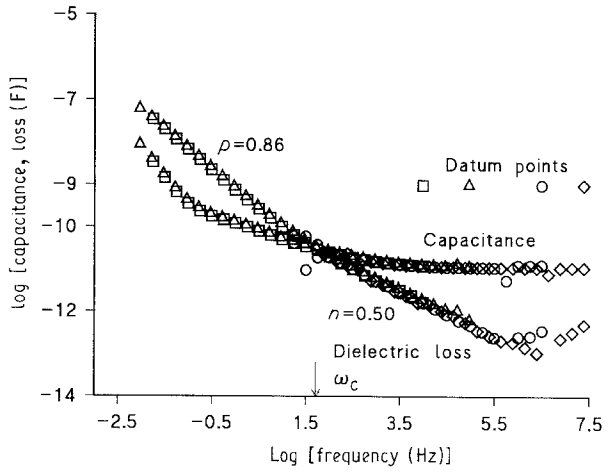

Figure 3 Dielectric response of solid PEG 3400, normalized to 323 K: (□) 323 K, (△) 313 K, (○) 293 K, (◇) 283 K.

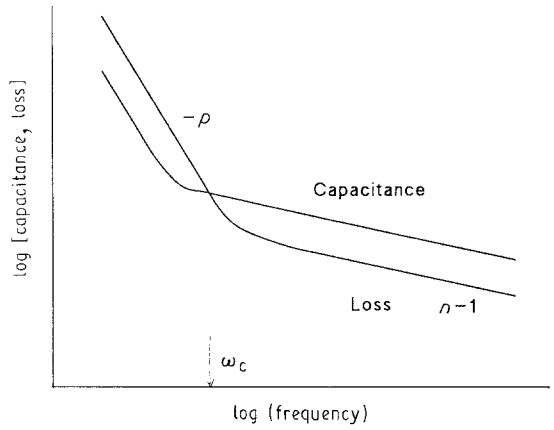

Figure 4 Schematic representation of low-frequency response of a solid material showing a typical QDC response (from Hill and Pickup [7]).

at frequencies below ω_c and

$$C(\omega) \propto G(\omega)/\omega \propto \omega^{n-1} \qquad 0 < n < 1 \qquad (2)$$

The spectrum shown in Fig. 3 differs from the ideal response in a number of ways. Firstly, the capacitance at low frequencies does not increase with the same slope as the loss, probably due to the surface electrode layer persisting into the solid. This will act as a further impedance layer, seen at very low frequencies in the same manner as described for the molten systems. Similarly, the high-frequency capacitance represents a truncation of the QDC response by a further polarization process, hence n has been measured via the loss slope above ω_c. The comparatively high value of p (0.86) approaches that of a d.c. conductivity, indicating that charge movement between clusters takes place relatively freely with a large path length between jumps. Similarly, the value of n (0.50) indicates a relatively low degree of correlation within the dipole clusters.

It has been suggested that the low-frequency response is associated with the amorphous fraction of the solid PEG, either as a result of hydroxyl groups within the amorphous fraction or alternatively due to the groups at the crystalline–amorphous interfaces [4, 15, 16]. A low value of n indicates a low degree of intra-cluster homogeneity which has been associated with the charge-carrying moiety being bound to a solid substrate [17]. These results therefore lend tentative support to the proposal of the hydroxyl groups protruding into the free amorphous fraction from the crystalline phase being observed, rather than the response of the amorphous region itself.

The effect of adding the drug on the solid response of PEG 3400 can be seen on examination of Table IV. The high-frequency conductance is greater for the solid dispersion than for the polymer alone, the increase being approximately tenfold. This may be due to the presence of dissolved drug in the solid or alternatively may be due to changes in the structure of the PEGs induced by the presence of the drug. It was noted that this increase was not seen for the equivalent molten PEG 3400 samples, implying that the change is due to alterations in the structure of the PEG itself. Previous studies using differential scanning calorimetry [5] have indicated that the heats of fusion of the PEGs decrease on inclusion of the drug, although the change is comparatively small. The increase in low-frequency response may therefore be a reflection of changes in the local environment in which the hydroxyl end-groups are embedded, possibly via a change in the distribution of amorphous and crystalline material through the sample.

The characteristic parameters associated with the response of the other molecular weight samples are also given in Table IV. Addition of the drug to the other molecular weight samples caused an increase in low-frequency conductance. Examination of the n and p values indicates that the value of p remained high and n remained low for all molecular weights. It is interesting to note that the value of n decreased with molecular weight, indicating a greater degree of cluster inhomogeneity with increasing chain length. It was also noted that the decrease in low-frequency conduct-

TABLE IV Characteristic values associated with the dielectric response of 10% nortriptyline HCl in solid PEGs

PEG mol. wt.	C (F) $\log f = 4$	Conductance (S) $\log f = -1$	Conductance (S) $\log f = 4$	$\log f = -1$	n	p
3400	1.231×10^{-11}	3.641×10^{-10}	1.068×10^{-7}	4.340×10^{-9}	0.50	0.86
6000	1.564×10^{-11}	5.466×10^{-10}	1.504×10^{-7}	3.004×10^{-9}	0.46	0.89
10 000	2.074×10^{-11}	5.408×10^{-10}	5.359×10^{-7}	2.573×10^{-10}	0.43	0.94
20 000	1.595×10^{-11}	3.470×10^{-10}	4.177×10^{-8}	1.183×10^{-10}	0.32	0.84

ance with increasing molecular weight seen for the PEGs alone [4] was also seen for the dispersions.

4. Conclusions

The study has demonstrated that low-frequency dielectric analysis may be used to study drug dispersions in polyethylene glycols in both the molten and solid states, giving information on the dielectric behaviour of disperse systems in general and on the structure of these dispersions in particular. In the molten state, the response is dominated by a bulk conduction mechanism (probably due to the presence of low molecular weight impurities) and a PEG barrier layer located at the electrodes. Evidence has been presented for the disruption of this barrier layer caused by the presence of the drug, shown by the change in capacitance slope compared to the PEGs alone. An understanding of the structure of this barrier layer is essential in order to interpret dielectric data in the kiloHertz region, as the capacitance slope in the frequency range up to 10^4 Hz may be determined by the structure of the barrier layer seen at < 1 Hz. Furthermore, the nature of the interaction between drugs and polymers in the molten state is poorly understood; hence these results are of more general relevance.

The solid response has been interpreted in terms of the Dissado–Hill theory [13] and an argument has been presented for the involvement of the amorphous fraction in the low-frequency response. While the exact mechanism involved has not been fully identified, the data presented here indicate that valuable information may be obtained using low-frequency analysis. The ability to study the distribution of amorphous material within a solid sample has a number of implications such as a greater understanding of the mechanical properties of semi-crystalline solids and the mechanism of release of drugs from polymeric matrices.

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