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A review of thermal methods used for the analysis of the crystal form, solution thermodynamics and glass transition behaviour of polyethylene glycols

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Abstract

The uses, properties and structure of polyethylene glycols are discussed, with particular emphasis on pharmaceutical considerations. The applications of thermal techniques in the characterisation of these materials in the solid or molten states and in aqueous solution are described. More specifically, the uses of differential scanning calorimetry, solution calorimetry, modulated differential scanning calorimetry, dynamic mechanical analysis and dielectric spectroscopy are outlined and the relative merits of the techniques discussed.

Keywords: Calorimetry; DMA; DSC; MDSC; Polyethylene glycol; Polymorph

1. Introduction

Polyethylene glycols (PEGs) are water soluble synthetic polymers based on oxyethylene, with the general structure $H-[-O-CH_2-CH_2-]_n-OH$, where n is the number of repeat units. These materials are available in a wide range of molecular weights, ranging from liquids at room temperature (PEG 200–600), semisolids (PEG 1500), semicrystalline solids (PEG 3000–20 000 and above) and resinous solids for higher molecular weights ($>100\,000$). Their comparatively low price, favourable toxicity and water solubility have led to a number of uses, including applications as adhesives, as thickeners, as contact lens fluids, as foam stabilisers, as a means of friction reduction in aqueous solution, as plasticisers in paint films, as a component of packaging materials and as solubilising agents for drugs. They may

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also be used as matrices for fast-release dosage forms, whereby a poorly soluble drug is incorporated within the polyethylene glycol, resulting in the dissolution rate of that drug being considerably increased in comparison to conventional dosage forms [1,2].

In addition, PEGs have a number of properties which are of interest in the biopharmaceutical sciences. They may be attached to the surface of liposomes in order to prevent recognition by the immune system, thus prolonging the circulation time of the liposomes [3]. They are also known to cause fusion between cells [4] and may bind to proteins [5]. It is therefore of importance to have some knowledge of the structure and properties of these systems. Thermal analysis has been used extensively for this purpose and a number of studies, particularly using differential scanning calorimetry, have been described. However, a number of techniques which are less well established in the pharmaceutical area have also been performed on these materials and some of these will be outlined here, not only in order to shed light on the structure and properties of PEGs but also to provide a showcase for some of these techniques which are not widely used pharmaceutically.

2. Structure of PEGs

The structure of PEGs must be considered in terms of both the conformation of individual molecules in the crystalline state and the arrangement of those molecules into micro- and macroscopic structures. The structure of the individual molecules has been studied using a number of techniques, including X-ray diffraction studies [6] which suggested that PEG has a helical conformation consisting of seven chemical units and two turns in a fibre identity period of 19.3 Å. This structure has been confirmed by IR [7], Raman [8] and NMR [9] studies, amongst other techniques. More recently, scanning tunnelling microscopy studies have imaged the helical structure [10], finding the length of the seven unit sequence to be 20 ± 1.3 Å, which is in excellent agreement with the figure suggested by the X-ray diffraction studies [6]. On melting solid PEGs, the helical structure is lost and a liquid containing random coils is obtained [11]. The same study suggested that solutions in chloroform and methylene chloride contain random coils, while in aqueous solution the system retains the helical configuration, albeit in a less ordered form. Other evidence has suggested that PEG molecules may exist as high or low density aggregates in aqueous solution [12]; hence there is still some debate regarding the conformation in water.

In the crystal lattice, the PEGs are arranged as lamellae, with the chains existing in either extended or folded forms, the latter being metastable with respect to the extended chain conformation. In both cases, the hydroxyl end groups are rejected onto the outside of the lamellae [13–15]. The proportion of crystals in the folded or extended chain forms is highly dependent on the molecular weight, as indicated in Table 1 [16]. In melt crystallised samples, spherulites are formed from the lamellae which may be as large as 1 cm in diameter due to the low nucleation rate of the spherulites [17].

Table 1
Thermal stability of folded chain PEG crystals (from Ref. [16])

Sample	Number of folds	Crystal thickness/nm	Stability [a]
10000	1	31.51	S
10000	2	21.01	S
10000	3	15.76	U
10000	4	12.60	O
8000	1	24.53	S
8000	2	16.35	U
8000	3	12.26	O
6000	1	18.87	S
6000	2	12.58	O
4000	1	12.33	U
4000	2	8.22	O
3000	1	8.79	U O

[a] s is the scanning rate; S, stable in DSC for $0.5 \leq s \leq 32$ C min^{-1}; U, unstable in DSC for $0.5 \leq s \leq 32$ C min^{-1}; U O, unstable in DSC, only observed for $s \geq 8$ C min^{-1}; O, not observed by DSC with $s \leq 32$ C min^{-1}.

PEGs are semicrystalline and may contain a significant proportion of amorphous material, depending on the sample preparation conditions and molecular weight. Consequently, PEGs exhibit a glass transition temperature which depends on the molecular weight of the sample. Previous studies [18] have indicated that in the molecular weight range of 10^2–10^7 the glass transition temperature rises from approximately -98°C to a maximum of -17°C for PEG 6000 which is also the molecular weight which exhibits the greatest degree of crystallinity, after which the transition temperature decreases with molecular weight.

PEGs therefore present a number of problems with regard to their use and characterisation. The possibility of changes in both the degree of crystallinity and the crystal form of a sample depending on the preparation conditions, along with considerations of the glass transition behaviour and stability of metastable forms all indicate that it is necessary to thoroughly characterise the PEG samples in order to predict and understand product performance. Thermal techniques provide a convenient means of achieving this, provided that the difficulties associated with analysing such complex materials are appreciated.

3. Differential scanning calorimetry

A number of studies have been conducted which involve the application of differential scanning calorimetry to PEGs. This technique involves heating or cooling a sample at a linear rate and measuring the temperature and energy associated with any one of a range of thermal events. The technique is widely used within the pharmaceutical sciences and these applications have been reviewed by Ford and Timmins [19].

Differential scanning calorimetry (DSC) has proved particularly useful in the analysis of the polyethylene glycols because it is possible to differentiate between the various crystal forms using the technique. In a thorough study by Buckley and Kovacs [16], the authors examined the effect of a number of variables on the thermal behaviour of chain folded PEGs. In particular, they examined the stability of the different folded chain forms by studying the effects of scanning speed on the endotherms. For example, PEG 6000 was crystallised in the once folded chain form by selfseeding at 62.45°C. Subsequent crystallisation at 51.0°C showed only a single peak over a range of scanning speeds from 0.5°C min^{-1} to 32°C min^{-1}, indicating that this crystal form is stable under the conditions used. It was noted, however, that the melting point of the polymer increased with increasing scanning speed. This effect has frequently been observed and is believed to be a reflection of the thermal inertia of the specimen, i.e. at faster rates, the rate of heat penetration into the sample relative to the heating rate of the furnace is lower and hence the melting point increases.

In the case of PEG 4000, however, clear evidence was found for instability of the folded crystal form. The endotherms of samples examined under a range of scanning speeds are shown in Fig. 1. As the rate increases, the proportion of the

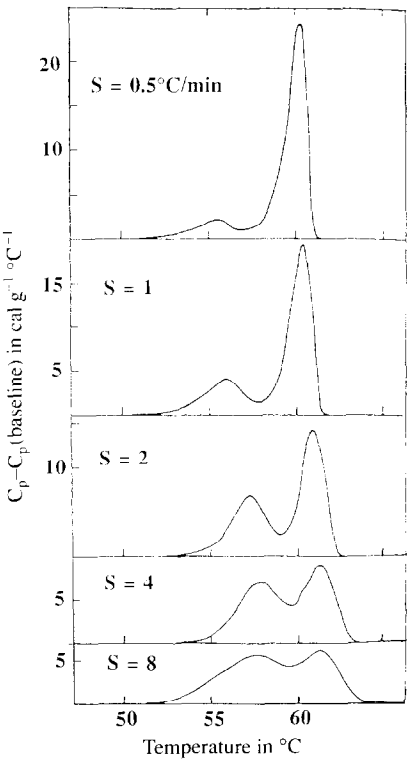

Fig. 1. Melting endotherms obtained at different heating rates (s) for PEG 4000, crystallised at 42.9°C in once folded chain form. Reproduced from Ref. [16] with permission. One joule is 0.239 calories.

unstable crystal form also appears to increase. This is because at the slower rates, the unstable crystals undergo stepwise unfolding during the heating process into the more stable form, while at higher scanning speeds, less time is available for this melt–recrystallisation reaction. A later study by Kambe [20] on PEG 4000 confirmed the presence of this reaction by demonstrating a crystallisation exotherm between the two peaks. The mechanism of chain folding has been discussed by Hoffman [21], who suggested that the degree of chain folding is dependent on the kinetics of the nucleation process, predicting that short chain molecules will require a far greater degree of undercooling than longer molecules for the chain folding process to be kinetically feasible. This is in agreement with the findings of Buckley and Kovacs [16] shown in Table 1, where the higher molecular weight PEGs showed a far greater tendency to chain fold that did the lower ones. These studies therefore highlight not only the complexity of PEG samples, but also the need for caution when interpreting DSC data.

The pharmaceutical importance of the crystal structure of PEGs has been highlighted in a number of studies. Beyene [22] demonstrated that moulded tablets of PEG had different tensile strengths, depending on the thermal conditioning used in their preparation. Chatham [23] later studied the effects of heating and cooling rates on the crystal structure of PEG 4000, particularly with a view to examining the effects on the dissolution rate of a model drug (trimethoprim) from solid dispersions. The author demonstrated that the dissolution rate of both the PEG itself and the drug is dependent on the thermal history of the dispersion. Craig and Newton [24] later studied the effect of heating and cooling conditions on a range of different molecular weight PEG samples, as shown in Table 2. As a technical point, the authors also noted that the thermal response was dependent on the particle size used, as large particles resulted in irregular and poorly reproducible peaks, almost certainly because of the poor thermal conductivity of the PEG samples and the poor contact with the pan leading to uneven heat penetration

Table 2
Melting characteristics of a range of PEG samples with standard deviations in parentheses (from Ref. [24])

Nominal molecular weight	Flash cooled samples		Slow cooled samples	
	Melting point/K	ΔH_F/ (kJ mol^{-1})	Melting point/K	ΔH_F/ (kJ mol^{-1})
3400	326.5, 331.6 (0.5) (0.3)	698.6 (30.9)	332.0 (0.5)	723.9 (15.4)
6000	329.1, 333.7 (0.4) (0.5)	1377.8 (17.2)	333.5 (0.3)	1463.4 (37.8)
10000	335.2 (0.1)	2722.7 (51.7)	335.9 (0.2)	3024.7 (13.6)
20000	335.7 (0.6)	3461.4 (95.5)	338.4 (0.2)	4264.2 (115.1)

through the sample. Interestingly, the authors did not find the same dependence of the release rate of a model drug (nortriptyline HCl) from the corresponding solid dispersions previously noted by Chatham [23], despite the presence of different chain forms for the slow and flash cooled samples [25]. This is probably due to differences in the flash cooling techniques used in the two studies, with Chatham [23] using a faster rate of cooling, thus producing a greater degree of amorphous material. The two studies therefore suggest that the dissolution rate may be more dependent on the degree of crystallinity than on the degree of chain folding. Chatham [23] also studied the effect of storage on the structure of PEG 4000, as drug dispersions in PEGs are known to show changes in dissolution rate over a period of time. The author showed that an increase in the heat of fusion is seen on storage of samples prepared under a range of conditions, indicating an increase in the degree of crystallinity. The author also noted an increase in the proportion of extended chain crystals within the solid on storage compared to the folded form, which is logical given the metastable nature of the folded chain crystals.

A further implication of the presence of different chain folded forms of PEGs lies in the interpretation of phase diagrams obtained by DSC. A number of authors have reported that drugs form eutectics with PEGs, with the eutectic corresponding to low drug concentrations. However, given that almost all the drugs under study melt at higher temperatures than do the PEGs, the melting behaviour of a drug in a pool of molten PEG may not be the same as that of a pure drug. Indeed, extensive peak broadening of the endotherm corresponding to the drug has been noted at low drug contents [26]. Consequently, it is difficult to envisage how the melting of the drug particles may be detected below approximately 10% w/w. Furthermore, it has been argued that what appear to be liquidus and solidus lines at low drug contents may in fact reflect the presence of two different crystal forms of the PEG [27].

4. Solution calorimetry

While the thermal properties of solid PEGs are clearly of importance, many of their pharmaceutical uses relate to their behaviour in solution. In particular, it is probable that the mechanism responsible for the increase in dissolution rate seen for drugs incorporated into solid dispersions lies in the interaction of PEGs with the drug in solution. Furthermore, a number of studies have shown that the presence of PEGs in solution may increase the solubility of drugs (see, for example, Ref. [28]). It is therefore necessary to have some knowledge of the solution thermodynamics of these systems, particularly the heat of solution (ΔH_s). This parameter is the heat evolved or absorbed when a solid is dissolved in a solvent. The value may be measured directly using solution calorimetry, which involves the dissolution of a known quantity of material in a known volume of solvent, held at a specified temperature in a dewar flask. A thermocouple within the flask measures the resulting heat change, from which the heat of solution may be easily calculated. This simple technique has many advantages over other forms of calorimetry. There

Table 3
Effect of heat treatment on the heats of solution of a range of molecular weight PEG samples with standard deviations in parentheses (from Ref. [38])

Nominal molecular weight	Heat of solution/kJ mol^{-1}		
	Untreated	Slow cooled	Flash cooled
3400	33.98 (0.76)	30.59 (1.40)	8.93 (0.37)
6000	90.73 (0.76)	57.53 (7.59)	31.22 (0.76)
10000	76.28 (5.07)	166.43 (7.60)	−28.61 (9.09)
20000	82.39 (3.11)	250.06 (15.53)	−120.68 (13.25)

is no invasive process involved other than the dissolution of the material. This is in contrast to DSC, whereby the results are usually obtained at elevated temperatures and extrapolated back to give an indication of the solid structure at room temperature. Furthermore, the technique may be used to yield information on both the solid structure of the material and the interaction of that sample with the solvent under study.

The solution properties of PEGs have been extensively studied [29,30] and a number of studies have examined their heats of solution. In particular, factors such as the molecular weight of the PEG [31–33], the nature of the solvent [34] and the crystalline–amorphous interfacial properties [35] have been studied. Liu and Parsons [36] have suggested that in aqueous solution, PEG forms a hydrated complex with three water molecules attached to each ethylene glycol unit, while Graham et al. [37] have studied the melting behaviour of PEG hydrates using DSC.

In a study aimed at more pharmaceutical considerations, Craig and Newton [38] investigated the heats of solution of PEGs 3400, 6000, 10 000 and 20 000 samples in water; the results are summarised in Table 3. The authors found that the technique was highly sensitive to the thermal history of the sample, much more so than DSC; hence the study indicates that solution calorimetry represents a sensitive method of detecting changes in crystal structure. The authors proposed a model whereby the heat of solution is considered to be a combination of the heat required to break the solid–solid bonds within the sample (equivalent to the heat of fusion) in addition to the energy of interaction with the solvent. The former process tends to be endothermic, while the latter is exothermic; hence the two cancel each other out to some extent, giving a small ΔH_s value relative to the heat of fusion. Therefore, when the ΔH_s values of two samples of PEG with different crystal structures are measured, the difference in the heat of solution between the two is proportionately greater than the difference in the two heats of fusion, even if the absolute energy differences are much the same for the two techniques. For example, the ΔH_s values for slow cooled and flash cooled PEG 10 000 are 166.43 and −28.61 kJ mol^{-1} respectively, hence clearly showing differences between the two. The heats of fusion for the same samples, however, are 3024.7 and 2722.7 kJ mol^{-1} respectively. The absolute differences between the two sets of figures are similar, but the proportion-

ate changes are very different. Given an approximate coefficient of variation of 2–3% for the two techniques, it therefore follows that, as a means of detecting changes in crystal form, solution calorimetry is more sensitive than DSC. This technique could therefore be usefully employed routinely as a means of detecting polymorphic changes in drugs and other materials. In addition, it is possible to calculate the heat of interaction of the individual PEG molecules with water, which may lead to a greater understanding of their solution behaviour.

5. Modulated differential scanning calorimetry

A further technique that is still comparatively unknown within the pharmaceutical (or indeed any other) field is modulated differential scanning calorimetry (MDSC). This technique represents an advancement in the software, rather than the hardware, associated with conventional DSC and early indications suggest that the modification may considerably extend the use of the technique. Conventional DSC measures the heat flux in and out of a sample as it is subjected to a linear heating programme. In MDSC, the underlying heating programme has a comparatively rapid sinusoidal oscillation superimposed upon it; hence the sample is experiencing both the gross change in underlying temperature which may be run at, for example, 2°C min^{-1}, but will simultaneously be experiencing a smaller, much more rapid heat change. By using a Fourier transform approach, it is possible to distinguish between the responses to these two heating programmes.

The signal obtained using conventional DSC incorporates responses to the heating programme which are both dependent and independent on the temperature of measurement, i.e.

$$dQ/dt = C_p\, dT/dt + f(t,T) \quad (1)$$

where Q is the heat evolved, C_p is the thermodynamic heat capacity, T is the absolute temperature, t is time and $f(t,T)$ is some function of time and temperature that governs the kinetic (temperature dependent) response of the sample. The response at any point in time may therefore be considered to consist of a temperature independent (reversing) component given by $C_p\, dT/dt$ and a temperature dependent (non-reversing) component described by $f(t,T)$. While these two components are virtually indistinguishable using conventional DSC, use of an oscillating signal allows separation of the two by analysis of the phase behaviour of the heat output with reference to the underlying heating rate. Kinetic processes such as crystallisation may therefore be distinguished from changes in the thermodynamic heat capacity, such as may be found, for example, in glass transitions.

The ability to distinguish the response to the oscillating heat change as opposed to the linear temperature rise allows an accurate measure of the heat capacity of the sample to be made, even at very slow or zero heating rates. The improvements obtained by using the modulated system compared to conventional DSC have been shown to be dramatic [39], because the method presents a means of measuring the

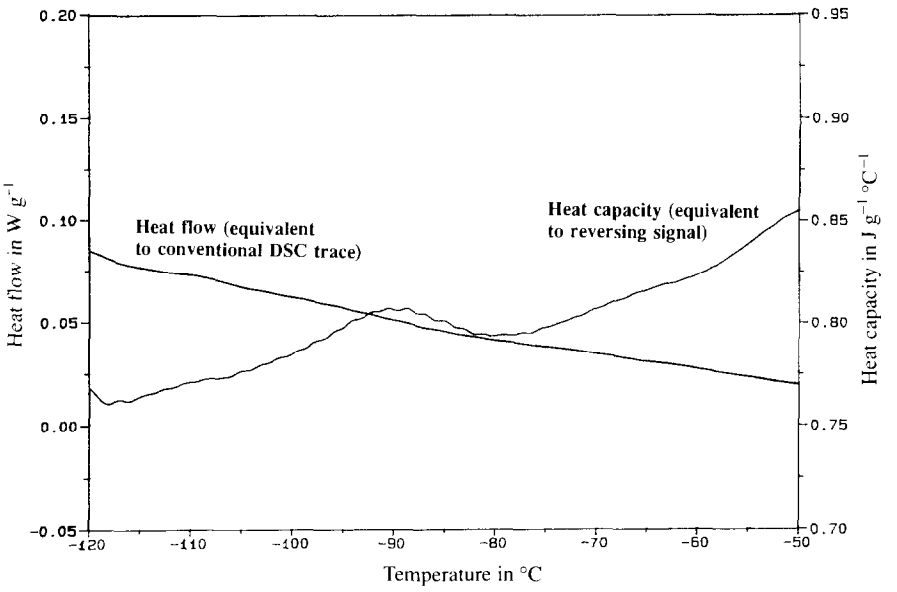

Fig. 2. MDSC analysis of PEG 4000. Run at 4 C min $^{-1}$, oscillation amplitude 1 C min $^{-1}$, 1 oscillation min $^{-1}$. The reversing component is equivalent to the heat capacity multiplied by the underlying heating rate (see Eq. (1)).

heat capacity directly, while problems such as baseline drift are considerably reduced, due to the cyclic response being virtually uninfluenced by the cell asymmetries which cause drift when using a simple linear heating programme. MDSC is particularly useful when studying glass transition phenomena, because in order to improve the signal-to-noise ratio using conventional DSC it is necessary to use a rapid heating rate, which in turn decreases the resolution. By using an oscillating signal, it is possible to measure the changes in heat capacity at a slow (or zero) underlying heating rate, thus considerably improving resolution.

The possibility of monitoring the thermodynamic heat capacity in isolation has led to the technique showing considerable promise in the study of glass transition phenomena [39]. So far, only preliminary studies have been conducted on PEG samples, but these results have proved encouraging. In particular, the low temperature transition behaviour of PEG 4000 has been studied, as shown in Fig. 2. The linear response of the sample (i.e. that corresponding to conventional DSC) shows no discernible discontinuity with temperature while a peak is seen in the cyclic heat capacity in the region corresponding to the glass transition. Clearly, much more work needs to be performed in order to clarify the phenomena seen here, but these initial results do support the claim [39] that this technique is superior to conventional DSC in detecting glass transitions and related phenomena. It is likely that this exciting new technique will become considerably more widely used in the study of pharmaceutical systems in the future.

6. Dielectric spectroscopy and dynamic mechanical analysis

Dielectric spectroscopy is a comparatively new technique to the pharmaceutical sciences and involves the application of an electric field to a sample, resulting in the polarisation of that material. When an alternating field is applied, the charges within the system will attempt to compensate for the changes in field direction by a number of mechanisms, including reorientation and charge-hopping. The overall effect will be the movement of charge within the sample, thus generating a polarisation current P. At any frequency, the relationship between the polarisation and the applied field will be given by

$$P(\omega) = \chi(\omega)E(\omega) \tag{2}$$

where (ω) denotes that the equation describes the relationship at frequency ω. The term χ refers to the susceptibility of the sample, which is a measure of the responsiveness of that material to an electric field. Under an alternating field, the term is complex due to the vectorial nature of the response, i.e. the relationship between the field and polarisation must be considered in terms of both the magnitude and the phase behaviour of the response, thus

$$\chi^*(\chi) = \chi'(\omega) - i\chi''(\omega) \tag{3}$$

where i is the square root of -1 and χ' and χ'' represent the real and imaginary components of the susceptibility, respectively. These two components may be considered to represent the energy stored and lost from the system. However, the susceptibility of a sample is an intrinsic property of that material and may not be measured directly. Using a cell containing electrodes of area A and separation distance d, the response may be conveniently expressed in terms of the capacitance C and dielectric loss G/ω (where G is the conductance) by

$$C = \frac{\varepsilon_0 A}{d}[\chi'(\omega) + \varepsilon(\infty)] \tag{4}$$

and

$$\frac{G}{\omega} = \frac{\varepsilon_0 A}{d}\chi''(\omega) \tag{5}$$

where ε_0 is the permittivity of free space and $\varepsilon(\infty)$ is the permittivity at infinite frequency. The conductivity G in Eq. (4) reflects the movement of charge due to reorientation of dipoles from one position to another (known as a.c. conductivity). In many systems, however, free charges exist which may move from one electrode to the other, thus generating a direct current $G_{\text{d.c.}}$. This may be accounted for by including a d.c. term in Eq. (5), thus

$$\frac{G}{\omega} = \frac{\varepsilon_0 \mathrm{A}}{d}\chi''(\omega) + \frac{G_{\text{d.c.}}}{\omega} \tag{6}$$

The capacitance and dielectric loss therefore give an indication of the real and imaginary susceptibilities, respectively. As dielectric behaviour is related to the

structure of a material, measurement of these two components over a range of frequencies yields spectra which are characteristic of the properties of that sample. Further details of the principles and uses of dielectric spectroscopy are available from a number of texts [40–43].

Dielectric measurements may be made either over a range of frequencies or, more usually for polymers, at one frequency over a range of temperatures, thus allowing thermal events, particularly glass transition phenomena, to be monitored. It is often used in this capacity in conjunction with dynamic mechanical analysis, which is described elsewhere in this journal [44]. This technique involves the measurement of the rheological properties of a sample over a range of temperatures; hence by using dielectric and mechanical analysis together it is possible to gain a more complete picture of the response of the samples as a whole.

The earliest and definitive studies using dynamic mechanical [18,45,46] and dielectric analysis [46–48] of PEG samples have been reviewed by McCrum et al. [49]. In a study by Read [18] on the dynamic mechanical response of a range of different molecular weight PEG samples, the G'' (loss modulus) plot shows one principal relaxation region at each molecular weight, while the logarithmic decrement (equal to $\pi \tan \delta = \pi G''/G'$) shows a second, higher temperature peak for the highest molecular weight sample, where G' is the storage modulus. This additional peak is designated α and the main peak β (Fig. 3). Ishida et al. [47] studied the dielectric

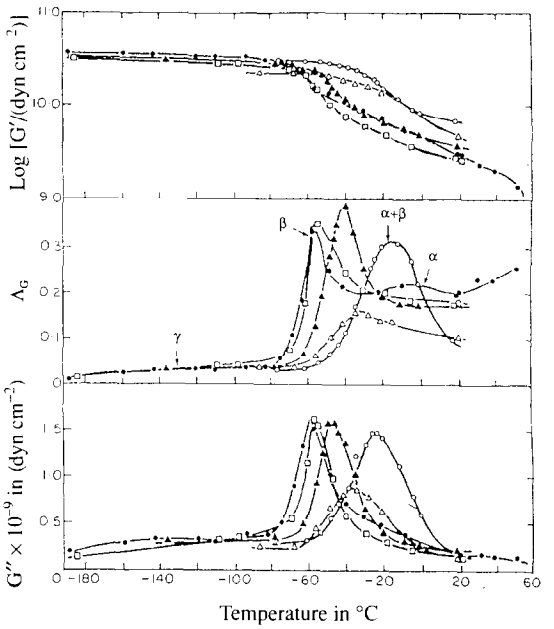

Fig. 3. G', G'' and logarithmic decrement Λ_G against temperature for PEG (0.5 Hz). Molecular weights are as follows: ●, 2.6×10^6; □, 8.4×10^5; ▲, 2.8×10^5; ○, 3×10^4; △, 4×10^3. Reproduced from Ref. [18] with permission.

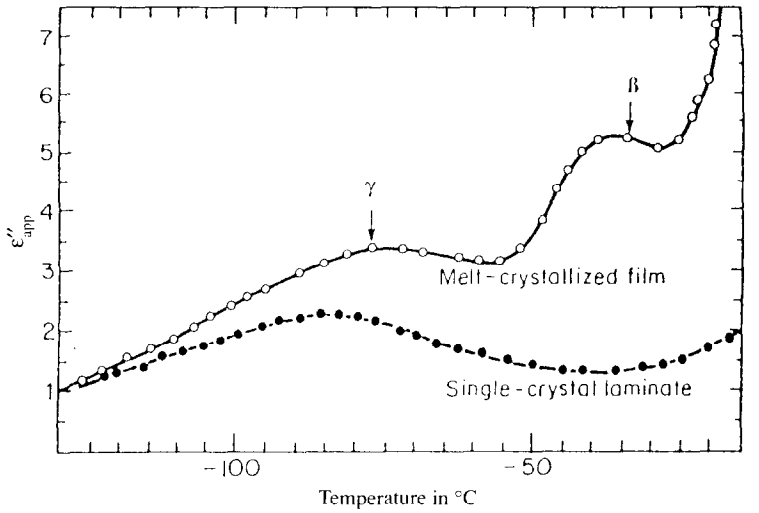

Fig. 4. Imaginary permittivity against temperature at 12.8 KHz for two samples of PEG. Reproduced from Ref. [47] with permission.

properties of melt-crystallised and single-crystal laminates, as shown in Fig. 4. The data is expressed in terms of the imaginary part of the permittivity ε'', which are related to the dielectric loss. Both samples show a low temperature γ response, while only the melt crystallised film shows the β response. The α process has been associated with the crystalline phase of high molecular weight polyethylene glycols [18], while the β process is associated with disordered regions of the PEG, as indicated by the absence of the β peak in the highly crystalline laminate [47]. It is therefore thought to be a reflection of the glass–rubber transition. The γ relaxation noted for the dielectric studies is associated with twisting of the main chains in the non-crystalline and crystalline regions of the sample [47]. These studies therefore indicate that dynamic mechanical analysis and dielectric analysis may be used in conjunction to characterise low temperature transitions in PEGs. As these transitions may be associated with product performance (e.g. modulus of the material at higher temperatures, plasticiser effects, etc.), the use of these techniques is of practical importance.

Studies have also been conducted in the frequency domain of PEG samples over a range of molecular weights. For example, Craig et al. [50] examined the lower frequency response of PEGs 3400 to 20 000 down to 10^{-1} Hz over a range of temperatures, including both molten and solid responses. The dielectric response in this low frequency region is known to be sensitive to changes in the crystal structure of the sample [23], although the exact mechanisms involved are not yet fully understood. The effect of drug addition to the PEG has also been studied [51], with an increase in the loss being seen which has been ascribed to dissolution of the drug within the polymer. This low frequency technique has clear potential as means of characterising PEG samples, both with and without drug.

7. Conclusions

This paper has discussed some of the work that has been performed in assessing the thermal properties of PEGs. In addition to their practical application within the pharmaceutical and other fields, these materials provide interesting model systems for the use of thermoanalytical techniques, as they may exist in different crystal forms and exhibit varying degrees of crystallinity. Any given PEG sample, therefore, may exist in a number of different structures, with correspondingly different thermal properties. This structural diversity may also prove disadvantageous, because not only does it imply that the manufacturing conditions used in the preparation of PEG products need to be carefully controlled, but it also means that care must be taken when interpreting thermoanalytical data.

The techniques described here may be classified as established in virtually all fields (DSC), not yet established in the pharmaceutical field but established elsewhere (solution calorimetry, dielectric analysis and dynamic mechanical analysis) or else not yet established in any field (MDSC). DSC is a highly versatile technique which, like any analytical method, suffers from some drawbacks, notably the invasive nature of the measurement and the difficulties associated with analysing multicomponent systems. Solution calorimetry has advantages in that it may yield information on both the solid structure of the sample and the interaction of that sample with water, but suffers from the disadvantage that the measured heat of solution is a reflection of several processes (solid bond breakage, interaction with the solvent, and possibly others); hence deconvolution of the results into these separate processes can sometimes be difficult. However, the results presented here and elsewhere strongly suggest that this technique is underexploited as a means of detecting polymorphism and could be used routinely in the development of new chemical entities. MDSC has clear potential as a means of understanding thermal processes more fully and could conceivably replace conventional DSC in the future, as it offers information which supplements, rather that replaces that provided by DSC at present. However, much more work is required in order to clarify the interpretation of the results and studies are ongoing to that effect. Finally, dielectric analysis and dynamic mechanical analysis are currently gaining ground as analytical techniques in the pharmaceutical field, as they may provide considerably more information on low temperature transitions than conventional DSC. In addition, these techniques are also being explored as means of characterising solids or gels under isothermal conditions; hence their use is not restricted to the detection of specific thermal events. Again, these techniques are likely to become more established within the pharmaceutical field in the future.

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