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Characterisation of polyethylene glycols using differential scanning calorimetry

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Summary

The melting behaviour of a range of different molecular weight polyethylene glycol (PEG) samples has been studied using differential scanning calorimetry (DSC). It was demonstrated that the shape of the endotherm was sensitive to the sample particle size, while the heat of fusion and melting points of the samples varied with scanning speed. Using standardised conditions, the PEG samples were solidified from the melt either by controlled cooling at 5 K/h or by immersing the sample in liquid nitrogen. The endotherms obtained indicated that the thermal history may determine both the degree of crystallinity and the crystal form of the polyethylene glycols, as shown by changes in the heat of fusion and melting points respectively. Studies using solid state nuclear magnetic resonance supported the conclusions drawn from the DSC studies. The study has therefore indicated that DSC is a suitable technique for detecting solid state changes in polyethylene glycols, thus facilitating standardisation of these materials.

Introduction

The polyethylene glycols (PEGs) are a series of water soluble synthetic polymers. The repeating unit is oxyethylene ($-OCH_2CH_2-$), with either end of the chain comprising an hydroxyl group. These substances are widely used as pharmaceutical excipients, being found in ointments, suspensions, capsules, tablets and suppositories (*Handbook of Pharmaceutical Excipients*, 1986). In addition, polyethylene glycols of the molecular weight range 3000–20000 are used as carriers for solid dispersion systems, whereby a poorly soluble drug is dispersed in a water soluble solid (Chiou and Riegelman, 1971). Formulation in this manner often leads to substantial increases in drug dissolution rate, although the mechanisms by which these increases occur are not yet fully understood.

The polymers in the molecular weight range used for solid dispersions are semi-crystalline, containing both ordered and amorphous regions. The chains are arranged as helices containing 7 monomers in a repeat unit (Tadokoro, 1966), the structure of the helices having recently been confirmed using scanning tunnelling microscopy

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(Yang et al., 1990). In the crystalline regions, the helices are arranged in parallel as plate-like structures (lamellae) from which the hydroxyl end groups are rejected onto the surface (Kovacs et al., 1975). The lamellae are in turn arranged in spherical structures (spherulites).

The PEG chains may be extended or folded within the lamellae. The folded chain crystals are metastable with respect to the extended chains, hence the melting points of the different crystal structures decrease as the number of folds increases. As the molecular weight of the PEG is raised, the kinetic stability of the folded chain forms increases. For example, PEG 10 000 has been reported to exist in up to five crystal types (i.e., extended and up to four times folded chain forms), whereas PEG 3000 may only exist in the extended or once-folded chain forms (Buckley and Kovacs, 1976). Being metastable, the chains may unfold over a period of time to yield the extended form (Chatham, 1985).

The usual method of manufacturing polyethylene glycol solid dispersions is to heat a mixture of the drug and carrier to the fluid state, upon which the melt is cooled to solidification. However, the conditions used to heat and cool the mixtures are frequently not controlled. The thermal history of a material may determine the solid structures of both polymers (e.g., Mandelkern, 1975) and drugs (e.g., Serajuddin et al., 1986). In particular, it has been demonstrated that the thermal history of the samples may affect the dissolution rate of both the PEGs themselves (Chatham, 1985) and of drugs dispersed in solid dispersions using PEGs as carriers (McGinity et al., 1984; Chatham, 1985). Moreover, the mechanical properties of PEGs, as assessed by diametral compression testing of moulded specimens, have been shown to be highly sensitive to thermal history and molecular weight of the samples (Beyene, 1981). It is therefore important to ascertain the relationship between the thermal history of PEG samples and the resulting solid structure in order to allow prediction of product performance.

In the present study, the crystal structure of a range of different molecular weight PEG samples, subjected to various previous heat treatments, will be studied using differential scanning calorimetry (DSC). Furthermore, the same samples will be analysed using solid state nuclear magnetic resonance (NMR) in order to corroborate the DSC data.

Materials and Methods

Characterisation of polyethylene glycols

Four samples of nominal molecular weights 3400 (Chemical Services Distribution Ltd (C.S.D.), Cheshire), 6000 (C.S.D., Cheshire), 10 000 (B.D.H. Chemicals, Poole) and 20 000 (B.D.H. Chemicals, Poole) were selected in order to examine a wide range of chain lengths and crystal forms. The same batch of each molecular weight sample was used for all experiments. The materials were supplied as flakes, but were ground and sieved for subsequent studies.

The molecular weight distributions of the samples were analysed using gel permeation chromatography (GPC). Measurements were taken at 353 K using a PL 2X mixed gel column (30 cm length, 5 μm average bead size). The average molecular weight values are given in Table 1. The polydispersity range of 1.081–1.116 was sufficiently low to consider the samples to be effectively monodisperse. The number average molecular weight values have been used for all subsequent calculations, although when referring to the different PEG samples in the text, the nominal values have been used.

Preparation of PEG samples

Heat-treated PEG samples were prepared as follows. 5 g of material were placed in 5.1 cm

TABLE 1

Molecular weight data obtained for polyethylene glycol samples using gel permeation chromatography

Nominal molecular weight	Number av. molecular weight	Weight av. molecular weight	Polydispersity values
3400	3690	4060	1.100
6000	7670	8330	1.086
10 000	14 900	16 100	1.081
20 000	20 700	23 100	1.116

stainless steel nipples with an internal diameter of 1.6 cm (Brown and Tawse Tubes Ltd, London), onto which stainless steel caps lined with PTFE were screwed. The tubes were placed in an LTE G150 Oven fitted with a Newtronic Micro 96 Digital Programmer (Laboratory Thermal Equipment, Oldham). The temperature was measured using a digital thermocouple and a mercury thermometer, both incorporated into the oven. The filled containers were heated from room temperature to 373 K at 3 K/min and held for 1 h. The samples were then either cooled slowly in the oven to 303 K at 5 K/h or flash cooled by immersing the containers in liquid nitrogen for 5 min. Flash-cooled samples were then stored over phosphorus pentoxide (B.D.H. Chemicals, Poole) to reduce condensation as the containers warmed to room temperature. The samples were ground using a pestle and mortar and examined on the day of preparation, unless otherwise stated.

Differential scanning calorimetry studies

Studies were conducted using a DuPont 910 differential scanning calorimeter (DuPont U.K. Ltd, Herts.). The equipment was calibrated using indium (Koch-Light Ltd, Suffolk). Samples of 3.0–3.5 mg were weighed into aluminium pans (DuPont U.K. Ltd, Herts.) using a five figure balance (Sartorius Ltd, Belmont) and sealed non-hermetically. A scanning rate of 4 K/min was used for all samples unless otherwise stated. The melting point was taken as the temperature corresponding to the apex of the endotherm (Barrall, 1973). While other methods of assessing the melting point have been described, the apex method is arguably the technique of choice when overlapping peaks are present. The areas of the endotherm were measured using a graphics tablet (Apple Computer Inc., California). Specific heats of fusion were calculated using the equation:

$$\Delta H_{\mathrm{F}}(\mathrm{sample})/\mathrm{g} = \frac{\mathrm{area/g\ of\ sample}}{\mathrm{area/g\ of\ indium}} \times \Delta H_{\mathrm{F}}(\mathrm{indium})/\mathrm{g}$$

The corresponding molar values were obtained by multiplying these values by the molecular weight. The heat of fusion of indium was 28.41 J/g (3.27 kJ/mol) and the melting point 429.6 K (Barrall, 1973). All studies were repeated three times.

Solid state nuclear magnetic resonance studies

Wideline ^{1}H solid state NMR studies were conducted at 298 K on slow- and flash-cooled ground PEG samples using a Bruker MSL-300 spectrometer (Bruker Instruments Inc., Massachusetts), equipped with a 7.05 T magnet. While this technique lacks the resolution of ^{13}C solid state NMR, it is nevertheless applicable to a wider range of species and may yield information on the mobility of hydrogen atoms within the solid sample.

Results and Discussion

Preliminary studies

Studies were conducted using untreated PEG samples in order to determine a suitable experimental protocol for subsequent investigations. Firstly, the effects of sample particle size were investigated. Secondly, the scanning speed was varied to allow comparison with the values obtained at 4 K/min.

Particle size effects While DSC is widely used in the analysis of solid dispersions, the sample particle dimensions are rarely stated. Studies were therefore performed to determine whether particle size has a significant effect on the melting endotherms. Samples were examined as received from the manufacturer (i.e., as flakes) and after grinding and sieving. Sieve fractions of 500–600 μm, 250–500 μm, 120–250 μm and < 120 μm were investigated.

In the majority of cases, the unground samples were found to give irregular and poorly reproducible endotherms. This may be due to poor thermal conductivity through the solid resulting in the sample melting into discrete areas within the pan, rather than undergoing a uniform transformation from solid to liquid (Barrall, 1973). These inhomogeneities may result in a broadening of the endotherm and the appearance of multiple peaks due to the melting process occurring over a range of temperatures.

Studies were then conducted on the ground samples. The < 120 μm PEG 3400 sample endotherm exhibited a shoulder on the leading edge of the endotherm. On increasing the particle size, however, the discontinuity became less pronounced. While the shoulder was small compared to the area of the endotherm, the above observations were found to be entirely reproducible.

The shoulder may arise for one of three reasons. Firstly, it may be an artefact caused by local thermal variations within the pan, as previously discussed. This explanation is not favoured as such variations are more likely to occur with the larger particle size samples and are unlikely to be reproducible. Secondly, the particles may be exhibiting a small pre-melting peak (Ubbelohde, 1978), this peak being swamped at higher particle sizes due to slower heat penetration through the sample. Alternatively, the disappearance of the shoulder at higher size fractions may be due to changes induced by the grinding process, resulting in different tendencies to exhibit pre-melting as the particle size is altered. Thirdly, the shoulder may indicate the presence of more than one crystal form within the sample, the disappearance of the discontinuity at higher size fractions again being due to thermal conductivity or grinding effects. Given the tendency of this molecular weight range of polyethylene glycols to exhibit chain folding (Buckley and Kovacs, 1976), this explanation is perhaps the most plausible. Similar particle size effects were also noted for PEG 6000 and PEG 10000. However, no changes in the endotherm shape were observed for the PEG 20000 samples. The 120–250 μm size fraction was used for all subsequent studies.

Scanning speed Samples of each molecular weight fraction were studied at scanning speeds of 2, 4 and 8 K/min, the values of the melting points and heats of fusion (ΔH_F) being given in Table 2. As the heat of fusion of indium was used as a standard, the literature value of 3.27 kJ/mol (Barrall, 1973) is given for each scanning speed. It was noted that on increasing the heating rate, the absolute areas of all the endotherms increased considerably, although a smaller change was seen in the areas relative to indium.

TABLE 2

Melting point (T_M/K) and heat of fusion (ΔH_F/kJ mol^{-1}) values of polyethylene glycol samples using various scanning speeds (standard deviations shown in parenthesis)

Molecular weight	Scanning speed					
	2 K/min		4 K/min		8 K/min	
	T_M	ΔH_F	T_m	ΔH_F	T_m	ΔH_F
3400	331.4	728.2	332.0	760.1	332.7	757.6
	(0.2)	(9.2)	(0.1)	(10.9)	(0.1)	(6.6)
6000	334.3	1471.8	335.2	1546.2	336.0	1613.0
	(0.7)	(26.3)	(0.3)	(30.9)	(0.4)	(62.9)
10000	335.1	2955.1	335.3	2913.0	335.5	2859.5
	(0.2)	(61.5)	(0.1)	(59.7)	(0.1)	(57.2)
20000	335.5	3953.1	335.6	3953.7	336.4	4033.1
	(0.1)	(49.4)	(0.3)	(47.0)	(0.2)	(96.0)
Indium	429.5	3.27	429.5	3.27	430.1	3.27
	(0.2)	(0.10)	(0.4)	(0.12)	(0.2)	(0.13)

The melting points given in Table 2 are taken directly from the experimental data and no recalibration was performed to take account of the changes in melting point of indium. There was an increase in the melting point and ΔH_F with scanning speed in most cases, especially for the lower molecular weight PEG fractions. Similar effects have been previously reported for phenylbutazone (Tuladhar et al., 1983). Buckley and Kovacs (1976) reported a linear increase in melting point with scanning speed for extended chain PEG 6000. A similar relationship was found for benzoic acid, *p*-nitrotoluene, indium and other commonly used melting point standards. These increases may be due to the finite melting rate of the crystals, thus leading to the measured temperature rising at a faster rate during the lag period at higher scanning speeds. A scanning speed of 4 K/min was used for all subsequent studies.

Examination of heat treated polyethylene glycol samples

Untreated samples The melting behaviour of the four molecular weight samples heated at 4 K/min is described in Table 2, while the endotherm for untreated PEG 3400 is shown in

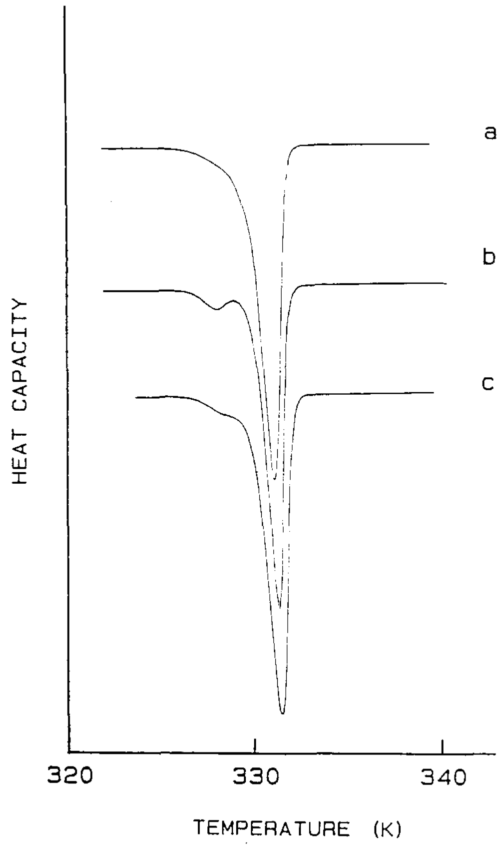

Fig. 1. DSC endotherm traces for PEG 3400. a, untreated; b, flash-cooled; c, slow-cooled.

comparison to those of the slow- and flash-cooled samples in Fig. 1. The observed melting points are similar to values stated in previous reports (e.g., Beech et al., 1972; Buckley and Kovacs, 1976), although it is not appropriate to make absolute comparisons as the thermal history of the samples has not been standardised in the present study. Moreover, the polymers exhibited a melting range rather than a specific melting point. This range may be dependent on the sample source as well as preparation conditions (Corrigan, 1986).

The melting points indicated in Table 2 show an increase with molecular weight between PEG 3400 and PEG 6000, after which the temperature of melting does not rise substantially. The values of ΔH_F showed a steady increase with molecular weight when calculated on a molar basis. However, the difference between the samples is considerably reduced when the heats of fusion are calculated on a weight basis. For example, ΔH_F values of PEG 3400 and PEG 20000 are equivalent to 205.89 kJ/kg and 191.05 kJ/kg respectively. These results are in reasonable agreement with those published elsewhere (e.g., Godovsky et al., 1972; Chatham, 1985; Ford et al., 1986).

Flash-cooled samples The melting behaviour of the flash-cooled samples is given in Table 3. PEG 3400 and PEG 6000 both showed double peaks, as shown in Fig. 1 for PEG 3400. Comparison of Tables 2 and 3 indicates that the melting point of the larger of the two PEG 3400 peaks is similar to that of the untreated sample. It is therefore reasonable to assume that these two endotherms represent the same crystal form. Furthermore, as the metastable form has a lower melting point than the extended chain crystal, it is also reasonable to assume that the lower and higher melting peaks represent the once-folded and extended chain forms respectively.

In all cases, the values of ΔH_F were lower for the flash-cooled than for the untreated samples. This is to be expected as the flash-cooling process results in a rapid crystallisation rate, causing a considerable reduction in short range order within the sample (Corradini, 1975). As the value of ΔH_F is largely a measure of the energy required to separate monomer units within the crystal structure (i.e., the degree of crystallinity), the

TABLE 3

Melting points and heats of fusion (ΔH_F) for flash- and slow-cooled polyethylene glycols (standard deviations in parenthesis)

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

overall enthalpy of fusion will decrease on flash-cooling. However, metastable crystals may recrystallise into the extended chain form immediately after melting, as reported for PEG 4000 (e.g., Kambe, 1980). This effect appears to be molecular weight dependent, with PEG 4000 showing a considerably greater degree of unfolding than PEG 6000 (Buckley and Kovacs, 1976). As there is no reason to assume that the energetics of the melting and crystallisation processes are equivalent, the ΔH_F data for the flash-cooled samples may not be considered entirely indicative of the solid structure at room temperature.

Both the melting points for flash-cooled PEG 6000 were lower than that given in Table 2 for the untreated sample. The endotherm seen for the untreated sample may therefore correspond to the extended chain crystal, while the two peaks for the flash-cooled sample may correspond to the once and twice folded crystal forms respectively.

PEG 10 000 yielded only one endotherm, this having a melting point very similar to that of the untreated sample. It is therefore likely that the crystal form of the two samples has remained unchanged. Flash-cooled PEG 10 000 has been reported to exist in a three times folded chain form at room temperature (Buckley and Kovacs, 1976), hence it is possible that this chain form is being observed in the present case. A similar set of observations was made for PEG 20 000, this molecular weight fraction showing no significant change in melting point.

Slow-cooled samples The results for the slow cooled systems are shown in Table 3. In each case, only one endotherm was seen. The PEG 3400 sample exhibited a melting point which, in view of the previous arguments, represents the

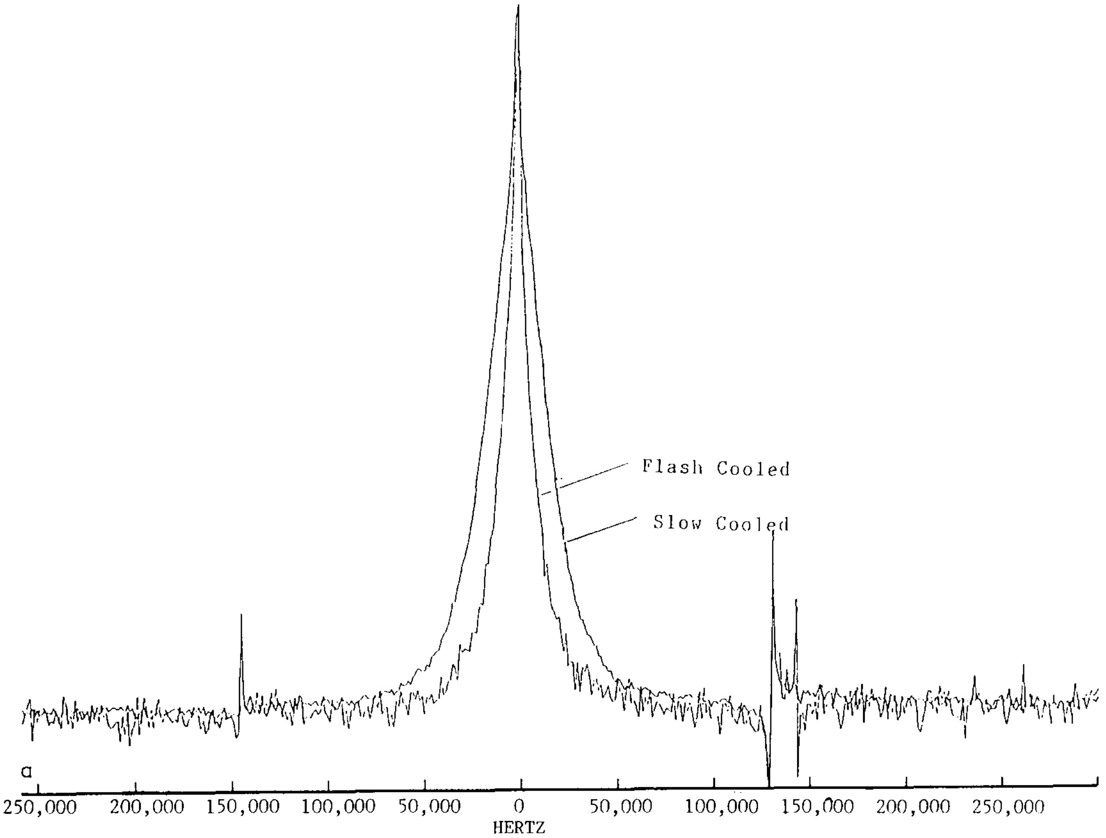

Fig. 2. ^{1}H wideline solid state NMR studies on slow- and flash-cooled PEG samples. a, PEG 10 000; b, PEG 20 000.

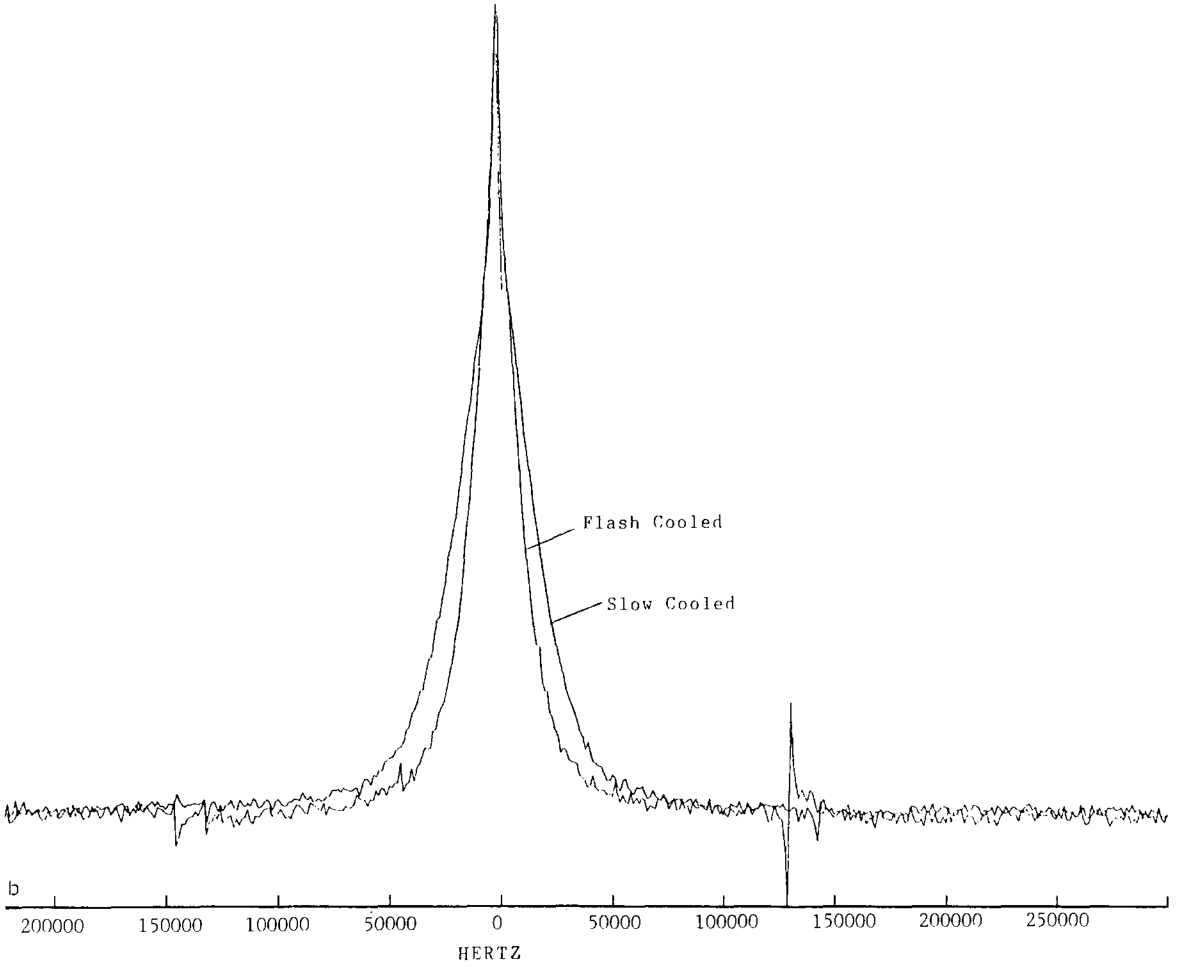

Fig. 2b.

extended chain crystal form. The ΔH_F value was lower than that seen for the untreated sample, but higher than that of the flash-cooled material. It can be seen from Fig. 1 that the melting endotherm exhibited a shoulder, which could correspond to the presence of folded chain crystals. It was also noted that this shoulder was considerably reduced in size after the sample was stored for 24 h at room temperature. PEG 6000 showed a lower value of ΔH_F than the untreated sample, the endotherm corresponding to the once-folded chain form.

The predominance of the chain folded forms in the flash-cooled as opposed to slow-cooled PEG 3400 and PEG 6000 samples may be explained in terms of the temperature of crystallisation, which is likely to be lower for the flash-cooled samples due to supercooling. The ratio of growth rates of the folded to extended chain crystals increases on lowering the temperature of crystallisation (Beech et al., 1972; Buckley and Kovacs, 1976). The flash-cooled samples may therefore be expected to exhibit a larger proportion of folded chain crystals, which was indeed the case in the present study.

The slow-cooled PEG 10 000 samples yielded a slightly higher melting point than the flash-cooled and untreated samples, possibly indicating the presence of a different crystal form. The heat of fusion of the slow-cooled samples showed a slight increase compared to the untreated sample. The melting point of the slow-cooled PEG 20 000 was higher than that found for the flash-cooled and untreated samples, indicating the presence of a less folded crystal form. However, it is not possible to state the exact degree of chain-folding present in the given samples. As for PEG 10 000, the heat of fusion was greater for the slow-cooled sample than for the untreated sample.

Solid state NMR studies In all cases, differences were seen in the NMR spectra depending on the previous heat treatment, with the flash-cooled samples producing narrower spectra than the corresponding slow-cooled materials. Typical spectra are shown in Fig. 2a and b for PEG 10 000 and PEG 20 000 samples. While it is not possible to identify the different crystal forms from the given data, it can be seen clearly that the spectra are sensitive to the thermal history of the samples. Furthermore, the shape of the peak may be related to the degree of amorphous material within the samples, as the observed peak broadening has been ascribed to the relaxation of hydrogen atoms on the methylene groups within the ordered regions of the material (Tanner, 1981). The observed spectra therefore indicate that the slow-cooled samples have a higher content of ordered material than the flash-cooled materials, a conclusion which is in qualitative agreement with the heat of fusion data presented in Table 3.

Conclusions

These studies have indicated that the particle size of the sample and scanning rate used should be considered when designing DSC experiments. While the changes in peak shape between the ground and unground samples are clear, the differences between sieve fractions are more subtle, thus their importance will depend upon the use to which the data are put. However, the knowledge that changes in the endotherm shape may be seen for different particle size fractions could be relevant to the detection of polymorphs or in the determination of purity using DSC.

The melting point and molar heat of fusion of the PEG samples increased with molecular weight. The study has demonstrated the difficulty in deriving relationships between properties such as melting point and PEG molecular weight, as the crystal form of the PEG samples may not be equivalent. It is also noted that there are considerable discrepancies between the nominal and measured molecular weights of the PEG samples, implying that care must be taken when using PEG molecular weights in calculations.

Solid state NMR studies showed differences in the response of the PEG samples, depending on the previous heat treatment. The observed differences indicated a higher proportion of ordered material in the slow-, as opposed to flash-cooled samples, which is in agreement with the heat of fusion values obtained from the DSC studies. Previous investigations using powder X-ray diffraction have also shown differences in the spectra of PEGs, depending on the previous heat treatment (Chatham, 1985).

Evidence has therefore been presented for changes in the solid structure of PEGs depending on the thermal history of the samples. Previous studies (e.g., Beyene, 1981; Chatham, 1985) have shown that it is important to characterise the structure of the polyethylene glycols in order to standardise product performance. The present investigation has indicated that DSC is a suitable technique for this purpose.

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