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Characterization of PEGs using matrix-assisted laser desorption/ionisation mass spectrometry and other related techniques

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Abstract

Matrix-assisted laser desorption/ionisation mass spectrometry time of flight (MALDI-TOF) was used to estimate the average molecular weight of PEGs (polyethylene glycols). Only the molecular weights determined by the reflectron mode were used because of better resolution. The average molecular weights were: PEG 1500 (1638), 4000 (4129), 6000 (6343), 10 000 (12 774) and 35 000 (34 650). The melting behaviour of PEGs in the molecular weight range 1500–35 000 have been examined. Infrared spectra showed the appearence of a new weak band at 1326 cm^{-1} for PEG 12 774 which increased in strength with increasing molecular weight suggesting an increase in amorphous content. This was confirmed by differential scanning calorimetry (DSC) and X-ray powder diffraction (XPD). The decrease in the enthalpy of fusion and the degree of crystallinity above molecular weight 6343 suggested maximum crystallinity at this molecular weight. Generally untreated and slow cooled PEG exhibited higher enthalpies of fusion than quench cooled, suggesting that they are more crystalline. Scanning electron microscopy (SEM) showed a more pronounced spherulitic structure for untreated and slow cooled PEG 12 774, while small or imperfect spherulites were observed after quench cooling. This was supported by XPD. The crystallinity for PEG 12 774 increased from quench cooled (71.5%), < untreated (78.1%) to < slow cooled (81.5%). The enthalpies of fusion of untreated PEGs were higher than slow cooled PEG in the molecular weight range 1638–6343, while the reverse occurred for PEG 12 774–34 650. These PEGs exhibited a higher proportion of amorphous material initially as suggested by IR spectra and an increase in crystal perfection may occur during storage. © 1997 Elsevier Science B.V.

Keywords: Matrix-assisted laser desorption/ionisation mass spectrometry; Time of flight; Linear mode; Reflectron mode; Molecular weight; Polyethylene glycol; Infrared spectroscopy; Differential scanning calorimetry; X-ray powder diffraction; Scanning electron microscopy; Spherulitic structure

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1. Introduction

Polyethylene glycols are extensively used as excipients and carriers in solid dispersions. Molecular weight determination is mainly based on rheological measurement. Murphy et al. (1981) and Lai (1986) have reported that liquid chromatography (LC), gel permeation chromatography (GPC) and mass spectrometry (MS) has proved a valid tool for the molecular weight distribution of polyglycol oligomers.

Matrix-assisted laser desorption/ionisation time of flight (MALDI-TOF) mass spectrometry is a recently introduced soft ionization technique that allows desorption and ionization of very large molecules even if in complex mixtures. MALDI-TOF techniques were originally developed for proteins (Karas and Hillenkamp, 1988) and its extension to the characterization of synthetic polymers is still underway (Bahr et al., 1992).

In the crystalline state, the polyethylene glycol chain contains seven structural units, $[CH_2CH_2O]_7$, and two helical turns per fibre, identity period 19.3 Å. The crystallographic unit cell contains four molecular chains and is monoclinic. Single crystals of PEG are flat platelets, known as lamellae (Bailey and Koleske, 1976) and are arranged in spherical structures (spherulites). In the lamellae, polymer chains are either fully extended or folded, a small number times [n]. The chain ends projected onto the surface layers of the crystalline lamellae; n-folded chain crystals are metastable with respect to $(n-1)$-folded ones and even more so to extended chain crystals (Buckley and Kovacs, 1976).

PEG below $M_w = 4000$ crystallize in extended-chain lamellar crystals; $M_w \sim 6000$ may crystallize in both extended and chain-folded crystals and higher molecular weights probably form folded chain crystals only. The effect of the molecular weight and crystallization temperature have a marked effect upon the relative proportions of the two crystalline forms (Beech et al., 1972).

The fusion process is technically the least difficult method of preparing dispersions provided drug and carrier are miscible in the molten state. The melt is then cooled either naturally, control cooled or rapidly quenched in liquid nitrogen.

Chatham (1985) reported melting temperature and time in the molten state exerted a small influence on PEG 4000 morphology than did cooling rate. The temperature at which crystallisation takes place, or the degree of super-cooling, is directly proportional to the cooling rate (Buckley and Kovacs, 1976). At relatively low cooling rates, solid with relatively high crystallinities are obtained (Fraser et al., 1978). Conversely, at high cooling rates, solid of lower crystallinity is obtained.

Quenching PEG in liquid nitrogen may give rise to more amorphous material. There is less time for orientation and crystallization of the polymer chain, possesses the highest free energy and consequently the greatest solubility. Chatham (1985) reported great differences in the dissolution rate of trimethoprim from slow and flash cooled PEG 4000. This difference was also seen for the polymers themselves. Knowledge of their solid structure under different conditions of cooling is important. Depending on the cooling conditions, materials with different crystallinity may result and it is well known that amorphous and crystalline materials have different compaction properties (Morita et al., 1984).

The aim of this work is to characterize PEGs in the molecular weight range 1500–35 000 using MALDI-TOF mass spectrometry. To study the effect of the molecular weight and cooling rates on PEG samples using infrared spectroscopy (IR), differential scanning calorimetry (DSC), X-ray powder diffraction (XPD) and scanning electron microscopy (SEM).

2. Materials and methods

2.1. Materials

Six samples of PEG with labelled molecular weights of 1500, 4000, 6000, 20 000 were supplied by BDH Laboratory, Poole, UK, whilst PEG 10 000 and 35 000 were supplied by Merck Schuchardt, Germany. All samples were in the form of flakes.

2-(4-Hydroxyphenylazo)benzoic acid (HABA), 2,5-dihydroxybenzoic acid (DHB) and tetrahydro-

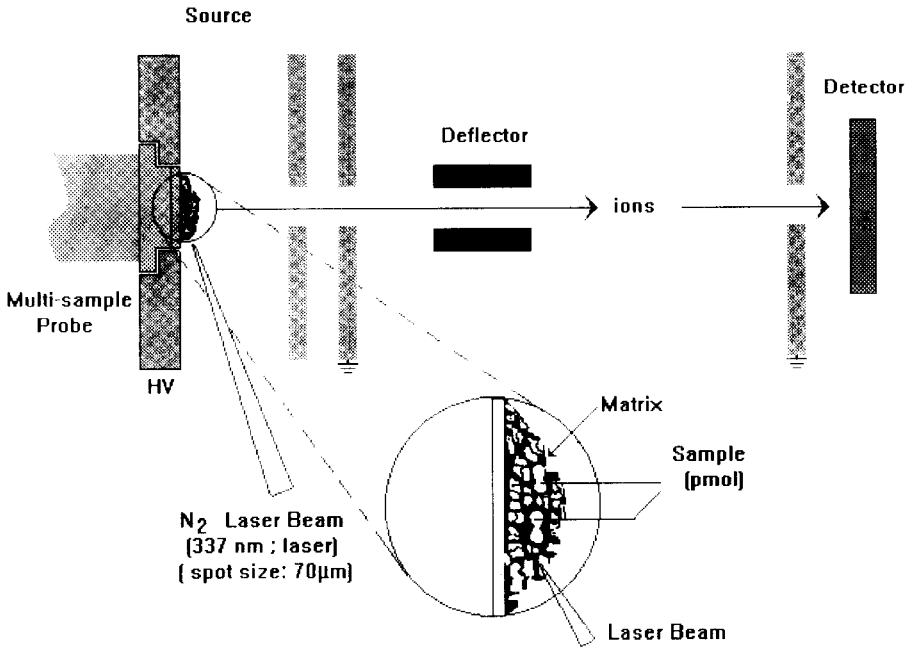

Fig. 1. Schematic of the linear TOF spectrometer.

furan (THF) were supplied by Aldrich, St-Quentin, France.

2.2. Matrix-assisted laser desorption/ionization (MALDI) sample preparation

The matrix solution was prepared by dissolving 12 mg of 2,5-dihydroxy benzoic acid in 1 ml of distilled water. A 1-μl aliquot of this solution was applied to the stainless steel sample slide and the solvent allowed to evaporate. PEG 1500, 4000, 6000 and 20 000 were dissolved in distilled water to obtain a solution of 100 pmol μl^{-1}. Then 1 pmol of sample solution was applied to the dry matrix and the matrix allowed to dry. For PEG 35 000 the matrix solution was prepared by dissolving 72 mg of 2-(4-hydroxyphenylazo)benzoic acid in 1 ml of tetrahydrofuran. PEG 35 000 was dissolved in hot THF to obtain a solution of 100 pmol μl^{-1}.

2.3. MALDI

A Finnigan MAT Vision 2000 (GmbH, Bremen, Germany) time of flight (TOF) mass spectrometer is equipped with a nitrogen laser at 337 nm and 5 ns pulse duration. The laser spot size was 70 μm and laser energy was adjusted close to threshold. The spectrometer has two detectors. The first detector operates when the reflectron device is off and allows the detection of ions in the linear mode (Fig. 1). The second detector is placed at the end of the second flight tube and allows detection of ions in the reflectron mode (Fig. 2).

2.4. Preparation of heat-treated PEG samples

First, 10 g of each PEG sample was prepared in duplicate. The temperature of the oven was adjusted to 100°C and the containers were held at this temperature for 30 min. One series were allowed to cool slowly to room temperature, while the others were quench cooled by immersing the container in liquid nitrogen for 20 min. Both slow and quench cooled PEG samples were stored over phosphorus pentoxide for 24 h. They were then carefully ground using a pestle and mortar and sieved. A sieve fraction of 250–350 μm was collected and examined within 48 h.

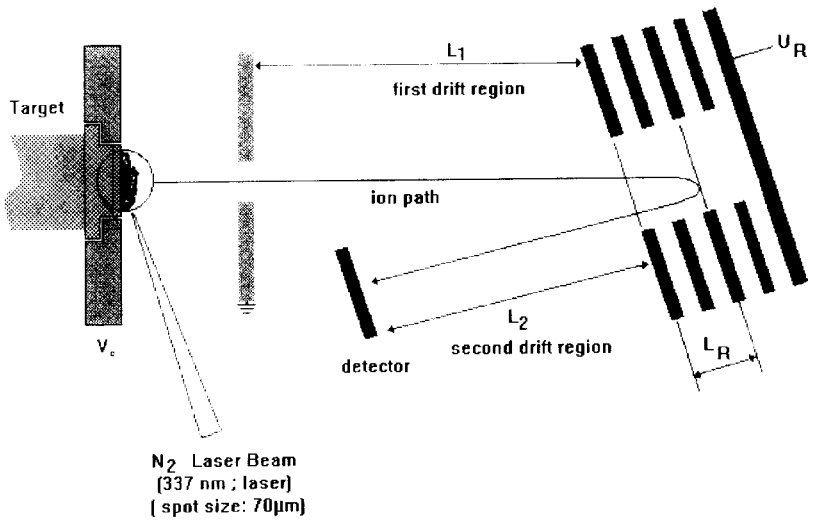

Fig. 2. Schematic of the reflectron TOF spectrometer.

2.5. Infrared spectroscopy

Infrared spectra were recorded using a Perkin Elmer FTIR 1600 spectrophotometer (Norwalk, Connecticut, USA) using KBr discs. These discs were made by grinding 2–3 mg of PEG with 25–50 mg of KBr and compressed (Model M-30: Industrial instruments, UK) at 10 tons for 2 min.

2.6. Differential scanning calorimetry

DSC measurements were carried out using a Model DSC-7 (Perkin Elmer, Beaconsfield, UK) controlled by a Perkin Elmer TAC7. The equipment was calibrated using indium and zinc. Samples of 4–6 mg of PEG (250–355 μm) size fraction were weighed to 0.01 mg and sealed into aluminium sample pans. A heating rate of 10°C min^{-1} was employed from 35 to 100°C in an atmosphere of nitrogen. Melting point and enthalpies of fusion were calculated [$n = 4$].

2.7. X-ray powder diffraction

X-ray diffraction spectra were obtained using a PW1729 fixed $\theta/2$ Goniometer with a PW 1710 Diffractometer (Phillips, Almelo, Netherland). The cavity of the metal sample holder was filled with the ground powder sample and smoothed with a spatula. A scanning rate of $0.04° \cdot 2\theta\ s^{-1}$ over the range from 10 to $50° \cdot 2\theta$ was used to produce the spectra.

3. Results and discussion

3.1. Molecular weight determination

Table 1 shows the suppliers labelled values for M_w and the results of the MALDI-TOF analysis in linear and reflectron mode. A straight line was obtained when linear and reflectron mode were plotted against the labelled values with a correlation coefficient $r = 0.9937$ ($df = 4$ $P < 0.001$). There was also an excellent correlation ($r = 0.9998$) between linear and reflectron mode molec-

Table 1
Suppliers labelled values for molecular weight of polyethylene glycol samples and those determined by MALDI-TOF mass spectrometer in linear and reflectron mode

Suppliers	Linear mode	Reflectron mode
1500	1702	1636
4000	4115	4129
6000	6327	6343
10 000	12 687	12 774
20 000	23 022	23 494

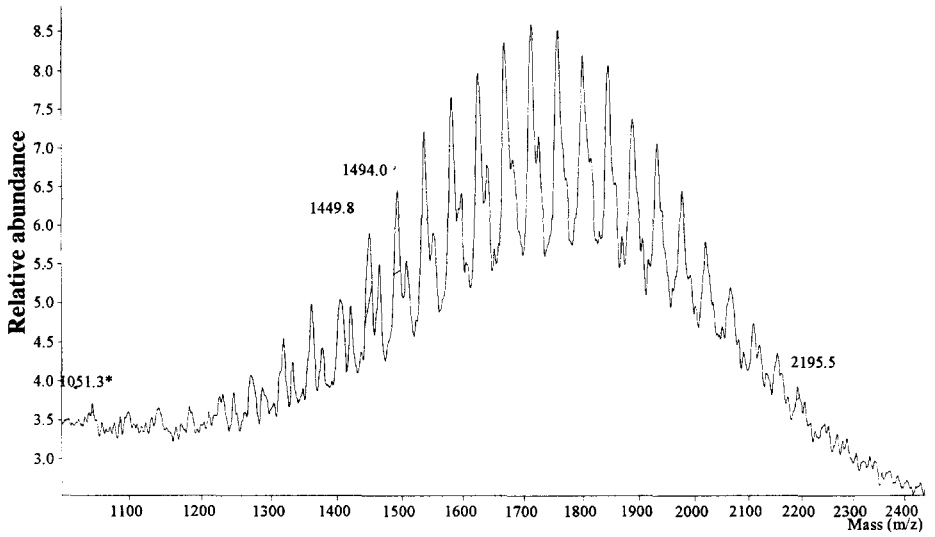

Fig. 3. MALDI-TOF mass spectrum of PEG 1500 using linear mode (average molecular weight determined was 1702).

ular weight ($P < 0.001$). Figs. 3 and 4 show MALDI-TOF mass spectrum for PEG 1500 in linear mode and reflectron mode, respectively.

The oligomer distribution of PEG 1500 was from 1050 to 2200 Da with a mass difference of 44 (CH_2CH_2O) between adjacent oligomers. The average molecular weights were 1702 Da (Fig. 3) and 1638 Da (Fig. 4). The peaks in mass spectrum correspond to the distribution of $[M + Na]^+$ and $[M + K]^+$ species. Since no dopant was used to promote cation formation, the sodium and potassium attached to the individual oligomers are present as trace impurities. As shown in Figs. 3 and 4 the resolution of the peaks in the reflectron mode is better than those in the linear mode. The reflectron TOF has an enlarged drift length, i.e. a longer time of flight and thus a larger resolution and were used for all subsequent studies.

3.2. Infrared spectroscopy

The infrared spectrum is extremely sensitive to the structure and conformation of a compound and can be used to compare different solid states (Byrn, 1982). The vibrations in the range 750–1600 cm^{-1} have been considered since this corresponds to the CH_2 vibrations within the polymer.

Fig. 5a–f show infrared spectra of untreated PEG in the molecular weight range 1638–34 650. Meares (1967) and Bailey and Koleske (1976) reported that the concentration, and hence the effect of the end groups decreases with increasing molecular weight, this can be seen from the infrared spectra. The band at approximately 880 cm^{-1} assigned to the vibration of the CH_2CH_2OH end group (White and Lovell, 1959) and decreases in intensity with increasing molecular weight. The band at 1115 cm^{-1} assigned to a hybrid of CO stretching and CH_2 rocking is down shifted by 18.2 cm^{-1} when molecular weight increases from 1638 to 34 650. A weak band appears at approximately 1326 cm^{-1} in the case of PEG 12 774 and increases in intensity as molecular weight increases. This band can be assigned to vibration in CH_2 wagging and is characteristic of the molten and amorphous state (Matsuura and Miyazawa, 1969). This may suggest that PEGs in the molecular weight range 12 774–34 650 contained more amorphous regions than lower molecular weight PEG. Tormala and Savolainen (1973) have shown that highest crystallinities occurred for PEG in the molecular weight range 4000–10 000. Bailey and Koleske (1976) and Ford et al. (1986) observed a maximum crystallinity around PEG 6000.

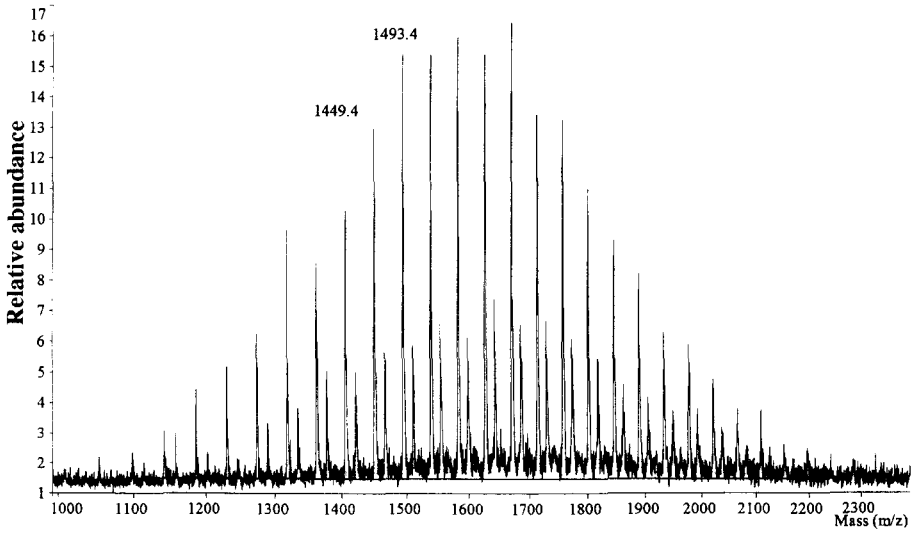

Fig. 4. MALDI-TOF mass spectrum of PEG 1500 using reflectron mode (average molecular weight determined was 1638).

3.3. Characterisation of untreated, slow and quench cooled PEGS by DSC

3.3.1. Effect of M_w and thermal history on the melting temperature

Table 2 summarises the melting behaviour of untreated, slow and quench-cooled PEGs. In all cases, the melting point increases with molecular weight up to PEG 23 494. Tukey's test showed that PEG 23 494 and PEG 34 650 had similar melting points. At higher molecular weights the melting point is determined by the thickness of the lamella rather than the length of the chains (Mandelkern, 1975).

The rate at which the polymer cools from the melt is an important factor in determining structure. Untreated, slow and quench cooled PEG 1638 exhibited only one melting transition at 47°C corresponding to extended chain lamella crystals (Beech et al., 1972; Buckley and Kovacs, 1976).

Untreated PEG 4129 exhibited one melting endotherm with a peak maximum temperature at approximately 62°C which corresponds to the melting of extended-chains (Bailey and Koleske, 1976). The shift down in melting point and broader endotherm for slow cooled PEG 4129 is consistent with an increase in amorphous material following fusion and recrystallization. Two melting transitions appear for quench cooled PEG 4129 at ~ 59°C and 62°C (Table 2). The melting point of the larger transition is similar to untreated and slow cooled PEG 4129, so these endotherms correspond to the extended-chain crystal and the lower transition could be assigned to the melting of folded chain crystals (Buckley and Kovacs, 1976; Craig and Newton, 1991).

Fig. 6 shows the melting behaviour of untreated, slow and quench cooled PEG 6343. All samples have one melting transition at approximately 63°C (Table 2). Evidently heating and crystallization have no effect. Both untreated and slow cooled PEG 6343 exhibited a shoulder at the edge of the peak. The shoulder could be due to the presence of folded chain crystals. The quench cooled PEG sample may therefore be expected to exhibit a larger proportion of folded chain crystals (Beech et al., 1972; Buckley and Kovacs, 1976; Craig and Newton, 1991). However, quench cooled samples showed one transition and no shoulder was observed (Fig. 6). Chain unfolding may occur during storage. However identical transitions were observed for fresh and aged samples. Quenching PEG 6343 in liquid nitrogen may favour the recrystallization of the metastable crystals into the extended chain form. This is not likely since the growth rate of once-folded chain

Table 2
Melting points (T_M) and enthalpies of fusion (ΔH_f) for untreated, slow and quench cooled polyethylene glycols (results are the means and standard deviations of four determinations)

Average molecular weight	Untreated samples			Slow cooled samples			Quench cooled samples		
	T_M (°C)	ΔH_F (J/g)	ΔH_F (kJ/mol)	T_M (°C)	ΔH_F (J/g)	ΔH_F (kJ/mol)	T_M (°C)	ΔH_F (J/g)	ΔH_F (kJ/mol)
1638	47.8	165.3	270.8	47.6	98.2	160.8	47.2	98.3	161.0
	(0.1)	(1.2)	(1.9)	(0.2)	(1.9)	(3.1)	(0.1)	(2.3)	(3.7)
4129	62.8	182.3	752.5	61.6	174.5	720.3	59.1/62.5	170.2	702.9
	(0.2)	(2.0)	(8.1)	(0.4)	(1.7)	(7.1)	(0.2)/(1.0)	(3.9)	(16.3)
6343	63.5	184.1	1167.5	63.4	177.6	1126.3	63.3	167.4	1062.1
	(0.5)	(1.2)	(7.6)	(1.0)	(4.8)	(30.6)	(0.3)	(1.1)	(7.2)
12 774	65.1	177.9	2272.1	67.5	184.3	2354.4	64.3	169.4	2164.0
	(0.3)	(2.7)	(34.6)	(0.1)	(0.3)	(4.3)	(0.2)	(0.4)	(5.2)
23 494	66.4	173.1	4065.9	69.3	184.3	4331.1	65.6	164.6	3867.5
	(0.3)	(1.7)	(39.0)	(0.3)	(0.7)	(17.6)	(0.4)	(2.1)	(49.9)
34 650	66.7	172.5	5977.5	69.5	176.5	6115.7	65.5	139.8	4843.8

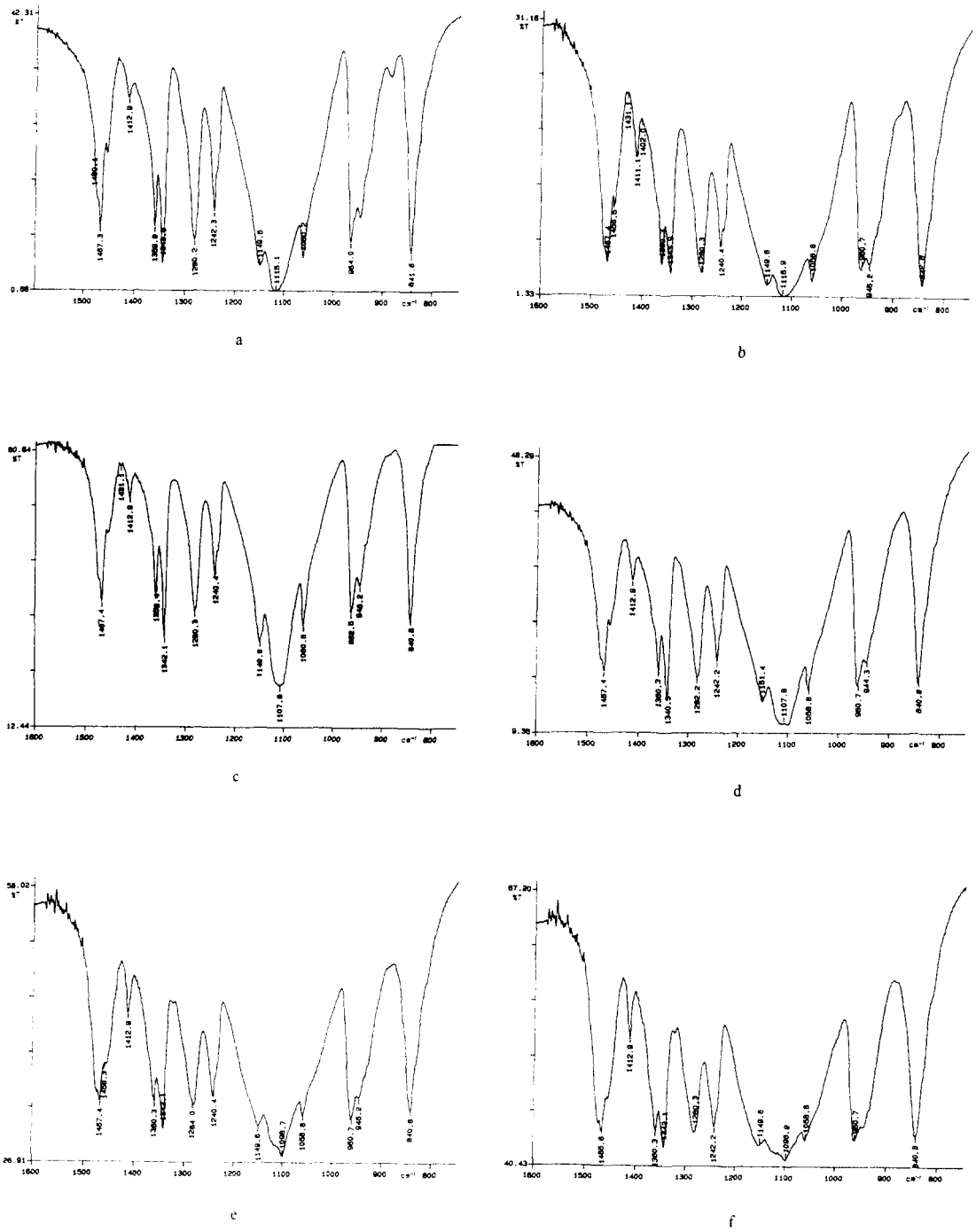

Fig. 5. Infrared spectra of untreated PEG: (a) 1638; (b) 4129; (c) 6343; (d) 12 774; (e) 23 494 and (f) 34 650.

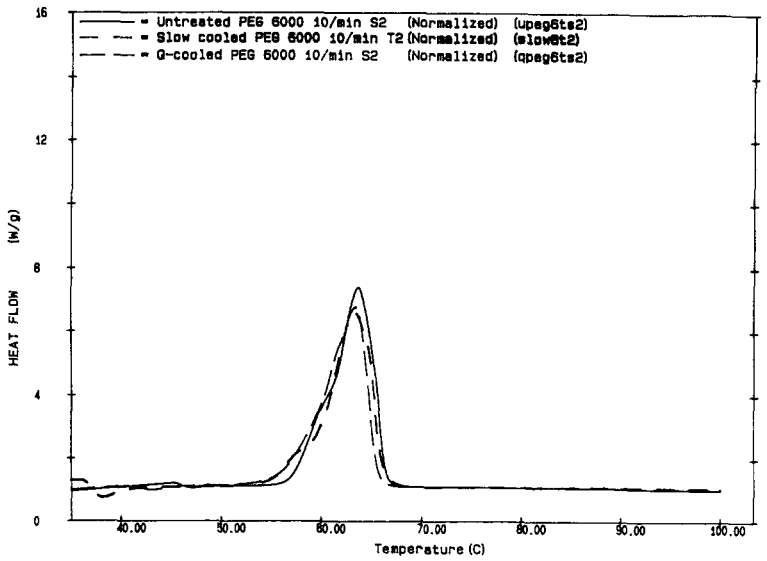

Fig. 6. DSC scans of untreated, slow and quench cooled PEG 6343.

crystals increases much faster with a decreasing temperature of crystallisation (Buckley and Kovacs, 1976). The chain may undergo unfolding during heating in the DSC, but this is more likely to occur with PEG 4129 which exhibited a greater rate of chain extension than once-folded PEG 6343 crystals (Buckley and Kovacs, 1976).

Untreated PEG 12 774 exhibited a shoulder, which disappeared for heat-treated samples. This may suggest that chain unfolding occurs during heating (Buckley and Kovacs, 1976). Slow cooled PEG exhibited a higher melting point than untreated and quench cooled PEG. This could be explained by the presence of less folded crystal forms [the disappearance of the shoulder] and an increase in crystal perfection which increases the melting point.

The increase in spherulite size is believed to be an increase in crystallinity. Photo-micrographs of untreated, slow and quench cooled PEG 12 774 are shown in Figs. 7–9. Untreated PEG (Fig. 7) shows a more pronounced spherulitic structure compared with the small or imperfect spherulites of quench cooled PEG sample (Fig. 9), while slow cooling produces larger, more brittle spherulites (Fig. 8). Thus was supported by XPD.

The rank order of crystallinity for PEG 12 774 samples was quench cooled (71.5%) < untreated (78.1%) and < slow cooled PEG (81.5%). A completely amorphous form could not be produced by immersing in liquid nitrogen for 20 min. Chatham (1985) reported similarly after immersing PEG 4000 in cardice or nitrogen.

Untreated and quench cooled PEG 23 494 exhibited the same melting transition, suggesting the same crystal form (Table 2). Slow cooled PEG exhibited higher transition than untreated and quench cooled PEG suggesting more crystal perfection and less folded chain crystal form. The observed melting points of untreated, slow and quench cooled PEG 34 650 were different. Slow cooled PEG exhibited the highest melting point

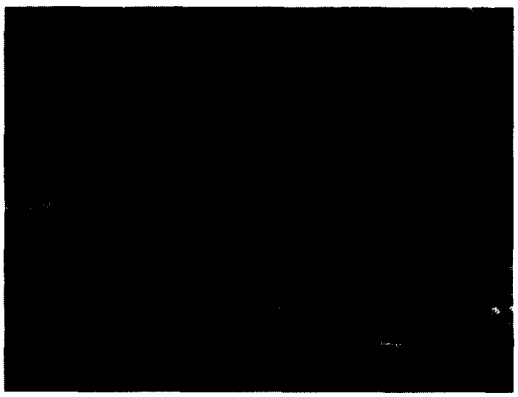

Fig. 7. Photomicrograph of untreated PEG 12 774, 250–355 μm sieve size (Magnification: × 750).

Fig. 8. Photomicrograph of slow cooled PEG 12 774, 250–355 μm sieve size (Magnification: × 750).

followed by untreated PEG, possibly due to the presence of a less folded crystal form and higher crystallinity.

3.3.2. Effect of molecular weight and the thermal history on the enthalpy of fusion

The enthalpy of fusion does not always increase with molecular weight on a weight basis (Table 2) reported by Ford et al. (1986) and Craig and Newton (1991). However there was always an increase in the enthalpy of fusion on a molar basis. Calculating the enthalpy of fusion on a molar basis may not be useful because some information on the degree of crystallinity may be lost especially when investigating different grades

Fig. 9. Photomicrograph of quench cooled PEG 12 774, 250–355 μm sieve size (Magnification: × 750).

of polymer. The observed decrease in the enthalpy of fusion above $M_w = 6343$ may reflect the decrease in crystallinity. To test this hypothesis, the degree of crystallinity was calculated according to the equation of Klug and Alexander (1974). The degrees of crystallinity of some untreated PEGs are: PEG 6343 (81.7%), PEG 12 774 (79.1%) and PEG 34 650 (75.5%). Indeed the decrease in the enthalpy of fusion observed above $M_w = 6343$ is due to a decrease in crystallinity. Furthermore, they can be related to the infrared spectra.

PEGs 1638–6343 have higher heats of fusion for untreated samples, while PEGs 12 774–34 650 have higher enthalpies of fusion for slow cooled samples than untreated and quench cooled. Craig and Newton (1991) found that untreated PEGs 3400–6000 exhibited higher enthalpies of fusion than both quench and slow cooled PEG, while slow cooled PEG 20 000 had a higher heat of fusion than untreated and quench cooled PEG with the same molecular weight. However no explanation was given. Ford et al. (1986) found that the heats of fusion of the recrystallized materials were lower than the untreated PEGs 1500, 4000 and 6000, while recrystallized PEG 20 000 exhibited a higher enthalpy of fusion than an untreated sample. Anguiano-Igea et al. (1995) found that recrystallized PEG 10 000 exhibited higher crystallinity than untreated PEG.

The higher enthalpies of fusion observed with slow cooled PEG compared to untreated and quench cooled PEGs 12 774–34 650 could be due to an increase in the ordered fraction during storage at room temperature. This molecular weight range is less crystalline than lower molecular weights as shown by infrared spectra and the calculated degrees of crystallinity. The quench cooled PEGs exhibited the lowest enthalpies of fusion suggesting a decrease in crystalline perfection.

4. Conclusions

Measurements of MALDI-TOF spectra in the linear and reflectron mode have been used to estimate the molecular weight of polyethylene glycols. Molecular weights provided by MALDI-

TOF correlate well with the labelled values given by the manufacturers. The reflectron mode gave better resolution of the peaks than linear mode because of the larger time of flight.

The enthalpy of fusion does not increase with increasing molecular weight on a weight basis. For untreated PEGs, the maximum value occurred around PEG 6343. The decrease in the enthalpy of fusion is due to a decrease in the crystallinity given by the infrared spectra and alculated degrees of crystallinity. This report supports previous findings that maximum crystallinity occurs at $M_w = 6000$.

These studies also show differences after heat treatment. Changes occur in melting point and enthalpy of fusion (from DSC). Generally, slow cooled PEG exhibits higher enthalpies of fusion than quench cooled PEG suggesting a higher proportion of ordered (crystalline) material. Quench cooling destroys the morphology of the spherulites and reduces the crystallinity, e.g. PEG 12 774.

The slow cooled PEGs 1638–6343 exhibited lower enthalpies of fusion than untreated PEG. This can be related to their inherent stability due to the presence of extended chain crystals and their greater resistance to the effect of ageing. The opposite was observed with PEGs 12 774–34 650. These PEGs are less crystalline initially, increasing their crystalline fraction after storage of 48 h. Higher molecular weight PEGs contain high proportion of folded chain crystal forms. The shift observed in their melting endotherm suggests that chain unfolding occurrs during storage. Thus, PEGs 12 774–34 650 may exhibit less resistance to the effect of ageing and this could dramatically decrease the dissolution rate of solid dispersion dosage forms.

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