Interaction of poly(ethylene oxide) with solvents: 3. Synthesis and swelling in water of crosslinked poly(ethylene glycol) urethane networks

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Polymer networks were prepared from poly(ethylene glycol) (PEG), methylene bis(4-phenyl isocyanate) and 1,2,6 hexane triol. By varying the amount of crosslinking agent (1,2,6 hexane triol) and the molecular weight of the PEG, a wide range of networks of different crystallinity and swelling were tailored and the influence of temperature and crosslinking on their swelling is discussed.

(Keywords: hydrogel; poly(ethylene oxide); synthesis; polyurethane; crystallinity; swelling)

INTRODUCTION

There is a substantial interest in synthetic hydrogels, of which various sorts are well known and have been described in literature. In particular homopolymers and copolymers of acrylamide[1], *N*-vinylpyrrolidone[2] and hydroxyethylmethacrylate[3] have been studied. A number of investigators[4,5] have produced hydrogel surfaces on conventional polymer substances by surface grafting. The homopolymer and copolymers incorporating low molecular weight blocks of poly(ethylene glycol) (PEG) in the form of crosslinked and thermoplastic block copolymer have been described in the patent literature[6–8] but little information appears to have been published on hydrogels of high crystallinity[9].

Water-swellable, water-insoluble hydrogels or xerogels as the dry materials are often called, may be synthesized from poly(ethylene glycol) or poly(ethylene oxide) by the following methods:

(1) Chemical crosslinking, which involves, for example, the chemical reaction of a polyfunctional monomer with poly(ethylene glycol)[7,10,11] or the radiation crosslinking of high molecular weight poly(ethylene oxide)[12,13].

(2) Entanglement crosslinking, which consists of dispersing high molecular weight poly(ethylene oxide) in a highly functional monomer and then polymerizing the monomer, thereby trapping the poly(ethylene oxide) in the matrix of crosslinked polymer formed from the monomer[13,14].

In the present study, the hydrogels were obtained by chemically crosslinking the poly(ethylene glycol) through urethane groups by incorporating a di-isocyanate and triol. Although considerable information can be found in literature[15–18] on the chemical crosslinking of poly(propylene glycol) through urethane groups, much less has been reported about the analogous poly(ethylene oxide)[19], though the use of poly(propylene oxide) end-capped with ethylene oxide and tetramethylene oxide is well known[20]. In this paper, part of a series on the topic, we report the synthesis, crystallinity and swelling characteristic of a series of poly(ethylene oxide) hydrogels. The nature of water in such materials is described in other publications of the series.

In an earlier paper[21] we reported the swelling characteristics of a hydrogel made from a poly(ethylene glycol) of number average molecular weight (M_n) 4200, trimethylol propane and Suprasec DN™, an aromatic di-isocyanate. The swelling characteristics and physical properties change quite dramatically with the presence and absence of crystallinity in the crosslinked polymer. Polymers of this type with no crystallinity are rubbers with rather poor tear resistance. On the other hand, those with ≈50% crystallinity are leathery, very tough tear resistant compositions. This contrasts with most hydrogels such as polyacrylamide[2], poly(*N*-vinyl pyrrolidone)[2] and poly(hydroxy methacrylate)[3], which are brittle in the dry state at ambient temperature.

EXPERIMENTAL

The polymer network system consists of a series of polyether urethanes based on methylene bis(4-phenyl isocyanate), poly(ethylene glycol) and 1,2,6 hexane triol as a crosslinking agent. The network would be expected to have the structure shown in *Figure 1*, with a minor presence of other groups such as allophanate not illustrated. The notation *n* and *m* in *Figure 1* represents the number of repeat units in PEG and the network respectively.

The great versatility of the system allowed the ratio of triol to PEG to be varied within fairly wide limits to obtain a range of compositions for study. The following naming system is used for identifying the various structural elements in a given polymer. The first number followed by letter M represents the ratio of the number of moles of 1,2,6 hexane triol to the number of moles of PEG (diol). PEG 6000, PEG 4000 and PEG 1500

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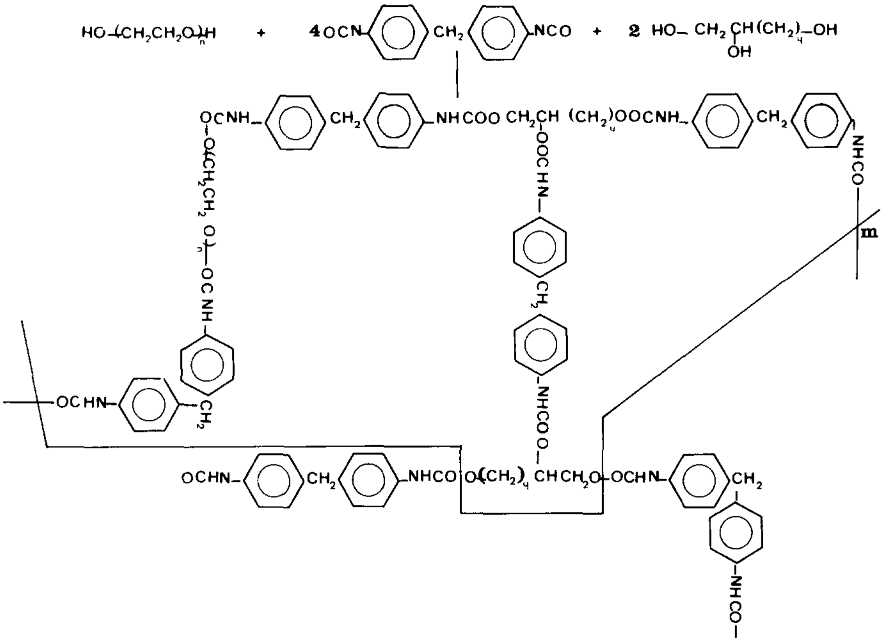

Figure 1 Representation of hydrogel network formation when a poly(ethylene glycol) and 1,2,6 hexane triol react with a stoichiometric amount of the methylene bis(4-phenyl isocyanate)

represent the commercial codes for the particular poly(ethylene glycol) and are identified with n in the formula. Thus, 1M-PEG 6000 is the hydrogel based on polyethylene glycol 6000 and methylene bis(4-phenyl isocyanate), crosslinked with 1 mol (equivalent to the actually measured M_n of PEG 6000) of 1,2,6 hexane triol. The term PEG is used for the oligomeric starting material containing terminal hydroxyls, while PEO is used when the hydroxyl groups have been reacted and the unit is an integral part of polymeric network.

Purification of materials

Methylene bis(4-phenyl isocyanate) (ICI) was distilled at 180–190°C (2 mm Hg) and stored in deep freeze ready for use. The molten PEG (Union Carbide) was passed through the charcoal column at 80°C to remove the residual catalyst. Further, it was dried at 110°C while simultaneously bleeding a stream of dry nitrogen for 4 h. The hydroxyl and acid numbers were determined by standard methods[22,23]. The number average molecular weight of polyethylene glycol (PEG) was determined by using the relation

$$M_n = \frac{112.2 \times 1000}{\text{hydroxyl number}}$$

The M_n for various PEG samples were thus found to be:

PEG 6000 = 8310
PEG 4000 = 3210
PEG 1500 = 1610

Thus, when incorporating a crosslinking agent and diisocyanate in the gel, the above M_n values were used to calculate the molar equivalent of diisocyanate and 1,2,6 hexane triol (Aldrich Chemical Co.), which was dried under vacuum at 80°C for 6 h and stored in a desiccator.

Formulation of hydrogel

Various molar compositions of 1,2,6 hexane triol were used to obtain different degrees of crosslinking in the poly(ethylene glycol) xerogels and a typical formulation is described below.

1,2,6 hexane triol (1.615 g) was added to 1 molar equivalent of PEG 6000 (100 g) in a beaker and maintained at 85°C. Molten methylene bis(4-phenyl isocyanate) (2.5 molar equivalents, 7.527 g) was poured into the mixture of glycol and vigorously stirred for 30 s before it was poured into a preheated Teflon mould and cured in an oven at 85°C for 4 h. When the mould cooled, the opaque off-white block of polymer was removed and stored in a dry atmosphere.

Procedure

The crystallinity and melting points of the various hydrogels were determined by using a Du Pont 990 thermal analyser with a Du Pont 910 differential scanning calorimetry (d.s.c.) cell. The melting point (T_m) was determined as the onset temperature from the corresponding melting endotherm. Normally, the heat of fusion of a polymer can be calculated by measuring the amount of heat required to melt the crystalline portions of the polymer and calculating the ratio of this value to that obtained from a 100% crystalline sample. As a 100% crystalline sample of the PEG base polyurethane could not be obtained, the heat of fusion of 100% crystalline PEG was used. The d.s.c. instrument was calibrated with pure indium metal ($\Delta H = 28.4\,\mathrm{J\,g^{-1}}$) (Ref. 24) as standard in order to obtain the heat of fusion of the xerogels. These values were compared with ΔH(fus) of 100% crystalline PEG[25] as 219.24 J g^{-1} to calculate fractional crystallinity. The percentage crystallinity was calculated by using the weight of crystalline fraction incorporated in the polymer test sample. For the swelling experiments, segments of known thickness and area were cut. The film thickness in all experiments was kept around 1 mm (0.9–1.1 mm). Films of known weights were swollen in distilled water and at intervals these were blotted dry with tissue and immediately weighed in a sealed sample bottle. Equilibrium swelling was taken after 24 h when no further increase in weight was noted.

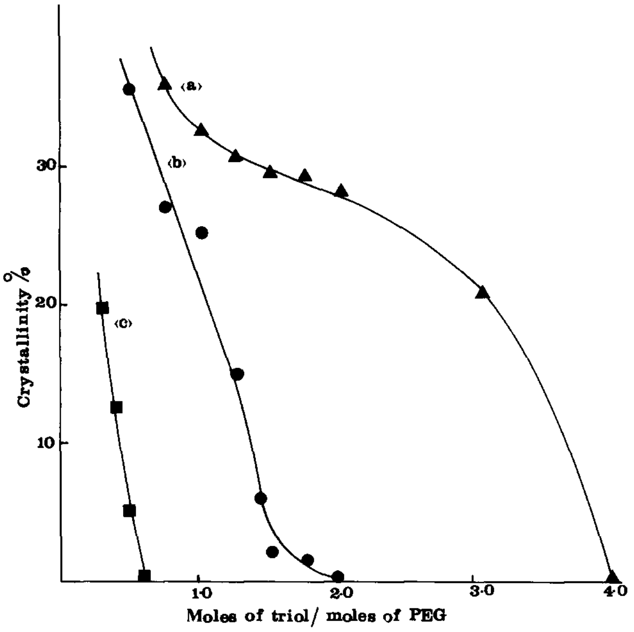

Figure 2 Crystallinity *versus* triol concentration: (a) hydrogel from PEG 6000; (b) hydrogel from PEG 4000; (c) hydrogel from PEG 1500

RESULTS AND DISCUSSION

The three series of hydrogels prepared from PEG 6000, PEG 4000 and PEG 1500 provided materials ranging from partially crystalline to completely amorphous. We expected that a knowledge of the swelling characteristics of these materials would lead to a better understanding of their use as drug delivery systems.

Crystallinity

Figure 2 presents the relationship between the crystallinity and the substrate ratio (triol/PEG) for the polyurethane xerogels. It is evident that with the increase of triol concentration in the polymer composition, the crystallinity is decreased. Pure PEG 6000 is 80% crystalline, while the xerogel containing 0.75 mol of triol is 42.7% crystalline. The crystallinity decreases gradually up to 3.0 mol of triol, but the polymer became completely amorphous when 4 mol triol were incorporated. Similarly, the hydrogel prepared from PEG 4000 became amorphous when 2.0 mol of triol were introduced into the network, but PEG 1500 only required 0.75 mol of triol to do so. The influence of molecular weight of PEG on the crystallinity of the xerogel is evidently due to varying degree of regularity because short glycol chains between the crosslinks have a smaller degree of freedom for their realignment in their space lattice, thus making the formation of a crystalline phase difficult or impossible. *Figure 3* shows that the crystalline melting temperatures (T_m) of the xerogels obtained from PEG 6000 are higher than those of PEG 4000 and PEG 1500. The T_m values thus follow the same order as the values for the linear precursor PEG, which are respectively 61, 55 and 45°C for PEG 6000, 4000 and 1500.

Flory[26] long ago pointed out that the T_m would be expected to decrease as the ratio of crystalline to amorphous volume decreased and this can be clearly seen in *Figure 3*, where the disruptive effect of increased crosslinking reduces the ability of the chains to form crystallites, which results in the reduction in crystalline melting temperature, for example PEG 6000 is 80% crystalline and melts at 61°C, while the xerogel, 0.75M-PEG 6000, which has 43% crystallinity, has a melting point of 46°C. The broken curve in *Figure 3* indicates the boundary limit between partially crystalline and amorphous polymer, i.e. if the triol/PEG ratio increases beyond the broken line, the crystalline polymers are no longer obtained. Sometimes, after many months or years of storage, samples in this amorphous region do slowly crystallize but the degree of crystallinity is small.

Swelling isotherms

The swelling of the xerogel samples in water was measured and the water uptake (parts per hundred parts of dry polymer, pph) was calculated using the following relationship:

$$(\text{pph}) = \left(\frac{W - W_0}{W_0}\right) \times 100$$

where W_0 = weight of xerogel and W = weight of hydrogel at equilibrium or at a certain time. The extractable material in the fully cured polymers was usually <2% and was not taken into account in the swelling calculations. Typical isotherms of 1M-PEG 6000, 1M-PEG 4000 and 1M-PEG 1500 at 25°C are shown in *Figure 4*. The equilibrium water uptake (pph) of 1M-PEG 6000 is 603%, 1M-PEG 4000 202% and 1M-PEG 1500 only 122%. The higher water uptake for the higher molecular weight poly(ethylene oxide) xerogel is associated with the longer chain of poly(ethylene oxide) between the crosslinks, which also produces higher degrees of crystallinity (*Figure 2*). This is the reverse of the situation for many crystalline hydrophilic polymers, e.g. cellulose[18], poly(vinyl alcohol)[27], poly(ethylene-terephthalate)[28] and nylon[29], where sorption of water in the crystalline polymers mainly occurs in the amorphous regions, as was shown by X-ray measurements of the lattice spacing, the crystallites remaining intact in the fully swollen polymer. The swelling with water thus decreases with increasing crystallinity. In poly(ethylene oxide) xerogel the crystallinity shows itself as opacity with a slight opalescence, and in the absence of crystallinity or phase separation the completely amor-

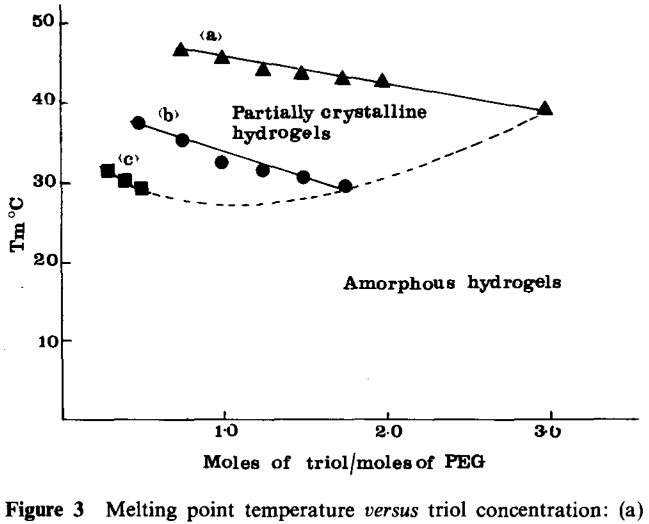

Figure 3 Melting point temperature *versus* triol concentration: (a) hydrogel from PEG 6000; (b) hydrogel from PEG 4000; (c) hydrogel from PEG 1500

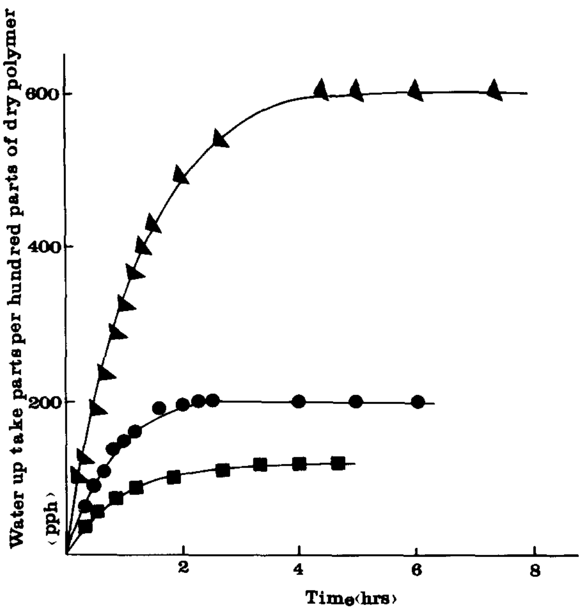

Figure 4 Swelling of various PEG hydrogels in water at 25°C: ▲, 1M-PEG 6000; ●, 1M-PEG 4000; ■, 1M-PEG 1500

phous but dry polymer is clear and transparent. When a thin slice is observed under a moderate magnification between crossed polarizers on a microscope, crystalline spherulites are clearly visible, as shown in *Figure 5a*.

During the swelling with water, the polymer becomes optically transparent. Under the microscope, as water advances into the polymer, the swollen/unswollen boundary is observed, and the spherulites gradually disappear (*Figure 5b*). This indicates that, in contrast to other crystalline hydrophilic polymers, in poly(ethylene oxide) xerogels the crystalline fraction is destroyed as the swellng proceeds. However, the presence of crystallites has been shown to affect the physical strength of these polymers[30]. Graham and McNeill[31] have shown that, after swelling in water and drying down, the network based on poly(ethylene oxide) recovers its original crystallinity, which in fact is usually 7% greater than that of the virgin polymer. This ability to recover and increase in crystallinity after swelling and redrying is evidence of a degree of potential order retained in the amorphous part of the dry polymer. The water-swollen crosslinked polymer as well as linear PEG aqueous solutions appears to have some order, which has been interpreted[21,30–33] as the presence of specific hydrates, namely mono and trihydrate. These complex formations in the PEO/H_2O system also make these networks different from those which are normally formed from hydrophilic monomers.

In view of the hydration process in PEO hydrogel, the swelling can now be visualized by considering a hypothetical model of the xerogel. In the dry state, regions of chain extended crystalline and amorphous PEO exist, held together by the hexane triol crosslinks. When water penetrates the network, the hydrophobic domain (triol + MDI) is pushed apart but still provides the matrix with a structural integrity. The crystalline and amorphous PEO chains become hydrated and stretched but, restrained by the crosslinks, retain some flexible yet ordered arrangement, creating a 'pore' structure through which water can penetrate freely. The swollen PEO chains are believed to contain water ordered into a specific trihydrate as well as free water in between[21,30,32]. In our work this water, believed to be bound as trihydrate, does not evidence itself by any obvious reduction in the expected diffusion characteristics. The time taken to attain equilibrium swelling of the hydrogels increases with the increasing molecular weight of the poly(ethylene oxide) between the crosslinker in the order 1M-PEG 1500 ($n = 36$), 1M-PEG 4000 ($n = 75$), 1M-PEG 6000 ($n = 188$), as can be seen in *Figure 4*. This can be explained in terms of amorphous and crystalline contents of the xerogels. The crystallinity increases in this series as follows: 0% (1M-PEG 1500), 25.5% (1M-PEG 4000), 31% (1M-PEG 6000) (*Figure 2*). It would be expected that the diffusion of water in the amorphous rubber phase would be faster than in the crystalline phase and the faster swelling of more amorphous polymers (1M-PEG 1500 and 1M-PEG 4000) is understandable. The amount of water in equilibrated hydrogel PEG 6000 decreased from 1110% to 350% as the crosslinking agent was varied from 0.75 to 2.0 mol, with respect to poly(ethylene glycol). Similarly, increasing the crosslink density in PEG 4000 and 1500 hydrogels produced a roughly parallel reduction in the equilibrium swelling, as shown in *Figure 6*. Increasing the crosslink density necessarily changes the composition, reducing the weight and molar percentage of polyethylene oxide. This, as well as the degree of crosslinking, must affect the ultimate attainable swelling. The first paper[21] of this series reported the dramatic decrease in aqueous swelling with increasing temperature of a poly(ethylene glycol) hydrogel of this class. The hydrogels described in the present paper were also observed at equilibrium at different temperatures. Two distinct features are observed with increasing

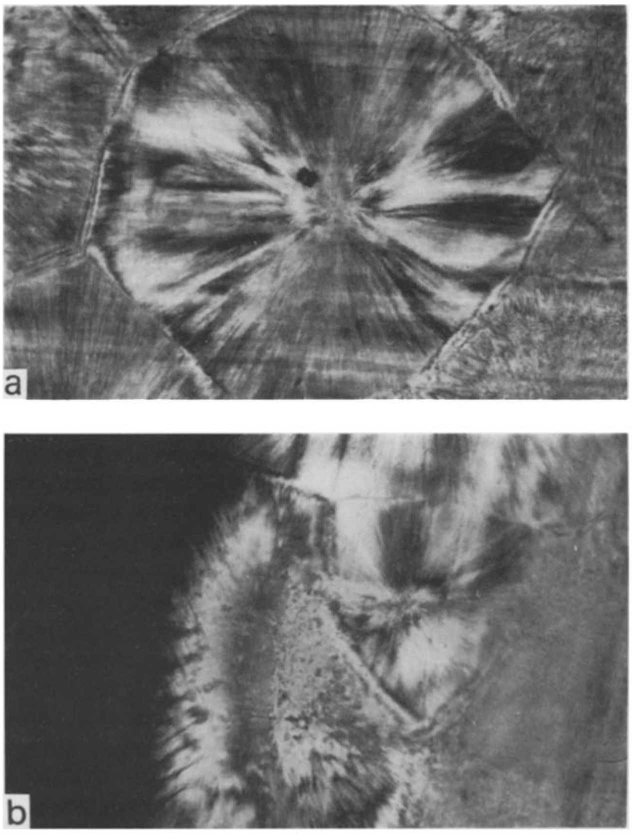

Figure 5 Photomicrographs of (a) 1M-PEG 6000 hydrogel film and (b) partially swollen 1M-PEG 6000 hydrogel film observed using crossed polarizers (magnification: ×25)

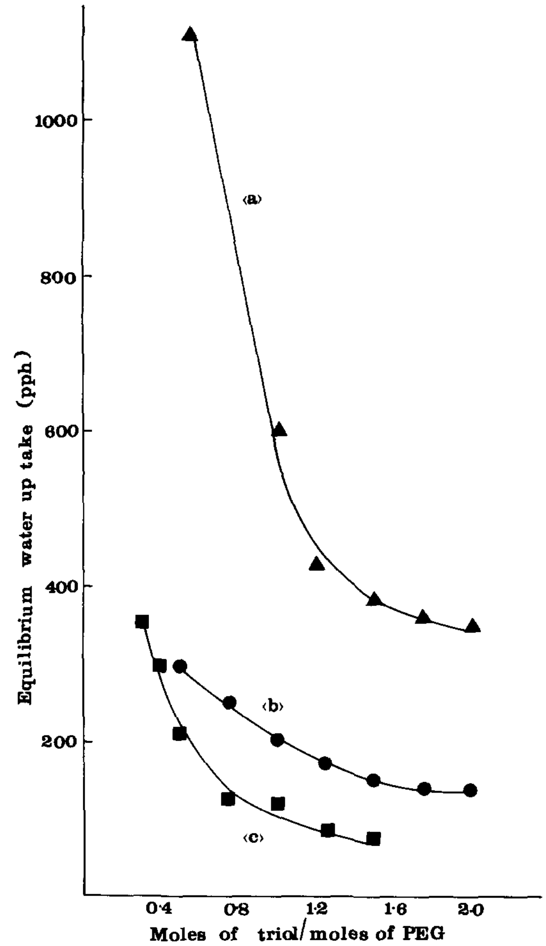

Figure 6 Effect of crosslinking agent on xerogel swelling at 25°C: (a) hydrogel from PEG 6000; (b) hydrogel from PEG 4000; (c) hydrogel from PEG 1500

temperature: a dramatic decrease in the equilibrium swelling value (*Figure 7*); and an increase in the rate of swelling (*Figure 8*).

Figure 7 shows the change of equilibrium water contents in 1M-PEG 6000, 1M-PEG 4000 and 1M-PEG 1500 hydrogels at 25, 37, 45 and 60°C. The broken lines in *Figure 7* indicate the syneresis of the corresponding hydrogel at 90°C after swelling to equilibrium at 25°C. It will be appreciated from *Figure 7* that for 1M-PEG 6000, the equilibrium swelling gradually decreases as the temperature is varied from 25 to 45°C, but a sharper reduction in the degree of swelling is observed as the swelling temperature is varied from 45 to 60°C. It is interesting to note that T_m of 1M-PEG 6000 is 45°C. In the first paper of this series[21] it was pointed out that the degree of swelling is directly proportional to negative reciprocal temperature, but careful examination of the related diagram in that paper suggests a break in the slope of the degree of swelling–temperature plot around the T_m of the hydrogel. The effect is very evident for the 1M-PEG 6000 and not present at all for the 1M-PEG 1500, as illustrated in *Figure 7*. This trend parallels the level of crystallinity in these polymers and the break occurs close to the crystalline melting temperatures. The effect may be due to the contribution of the free energy of fusion to the free energy of swelling. The contribution of the free energy of fusion will be zero above the dry crystalline melting temperature. In a previous publication[21] it was also pointed out that negative enthalpy of interaction of water with poly(ethylene oxide) is sufficient to melt the crystallites. The entropy change is, however, assumed to be negative[34] and hence the term $T\Delta S$ in the equation $\Delta G = \Delta H - T\Delta S$ has a negative value, so a rise in temperature decreases the free energy change ΔG and consequently swelling is reduced. The changes in the degree of swelling at higher temperatures can also arise from the breakage of the hydrogen bonds between water and polymer and the resulting change in the ΔH term. The syneresis in these PEO networks is also consistent with the cloud point observations for linear PEG/H_2O systems, where an inverse solubility–temperature relation is obtained[35,36]. As the temperature of an aqueous solution of high molecular weight linear PEG is raised to near the boiling point of water, the polymer precipitates. Though the equilibrium swelling of the hydrogels is decreasing with the temperature rise, the rate of swelling increases as shown in *Figure 8*. This is

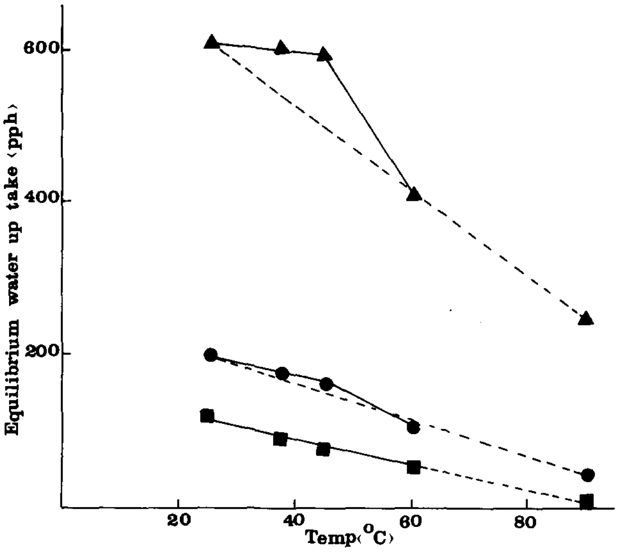

Figure 7 Effect of temperature on equilibrium swelling: ▲, 1M-PEG 6000; ●, 1M-PEG 4000; ■, 1M-PEG 1500. ---, Syneresis at 90°C after equilibrium swelling at 25°C

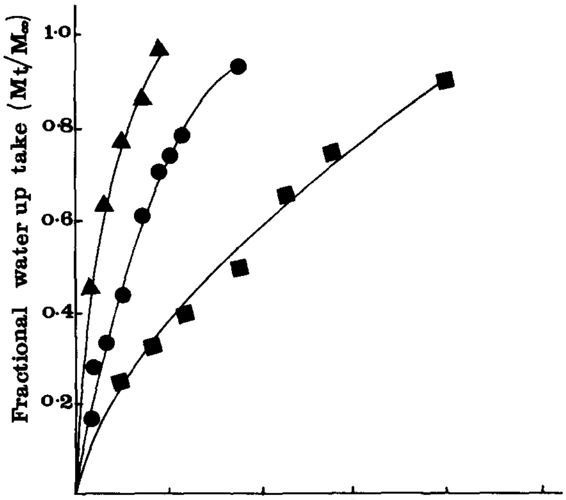

Figure 8 Fractional water uptake of 1M-PEG 4000 at various temperatures: ▲, 60°C; ●, 25°C; ■, 0°C

not surprising as diffusion rates increase with temperature. The system is, however, complex as the diffusion will occur much more rapidly through amorphous domains than through the crystallites[37]. As the crystallites melt between 25 and 65°C for the hydrogel in *Figure 8*, there will be a larger change in the rates of water diffusion in the swollen polymer between these temperatures than expected. It is thus not surprising that we were not able to obtain straight line Arrhenius type plots for the rate of uptake of water at the three temperatures investigated.

CONCLUSIONS

A wide range of hydrogels can be prepared from poly(ethylene glycol) of varying molecular weights ($1500 \lesssim M_n \lesssim 8300$) between crosslinks. Increasing the crosslinking density causes a reduction in both the crystalline melting temperature and the crystalline fraction in the hydrogels. All of the polymers exhibit a marked reduction in swelling in water with increasing temperature and the degree of swelling is reduced as the crosslinking is increased. The rate of swelling is increased at higher temperatures.

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