J Mater Sci (2007) 42:4136–4148
DOI 10.1007/s10853-006-0912-z

The synthesis, swelling behaviour and rheological properties of chemically crosslinked thermosensitive copolymers based on *N*-isopropylacrylamide

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Received: 30 June 2006 / Accepted: 1 September 2006 / Published online: 8 March 2007

Abstract In this contribution thermosensitive polymer matrices based on *N*-isopropylacrylamide have been developed. The hydrogels were prepared by photopolymerisation of *N*-isopropylacrylamide and 1-vinyl-2-pyrrolidinone in appropriate amounts of distilled water. The monomers were cured using a UV-light sensitive initiator called 1-hydroxycyclohexylphenylketone. These copolymers were crosslinked using ethylene glycol dimethacrylate and poly(ethylene glycol) dimethacrylate with molecular weights 600 and 1,000, at 0.1 wt% of the total monomer content. The chemical structure of the xerogels was characterised by means of Fourier transform infrared spectroscopy (FTIR) and the transition temperature of the hydrogels was determined using modulated differential scanning calorimetry (MDSC). By altering the feed ratio, hydrogels were synthesised to have lower critical solution temperatures (LCST) around 37 °C. This ability to shift the phase transition temperature of the gels provides excellent flexibility in tailoring transitions for specific uses. The samples synthesised with PEG1000DMA crosslinking agents absorbed over 18 times their weight in water, while maintaining good gel integrity thus falling marginally short of being characterised as superabsorbent. Each of the samples showed similar deswelling behaviour at 37 °C. Rheological studies showed that increasing the molecular weight of the crosslinking agent caused an increase in hydrogel strength.

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Introduction

Intelligent polymers are soluble, surface coated or crosslinked polymeric materials capable of undergoing sharp physical or chemical modifications in response to external stimuli such as temperature or pH [1]. Hydrogels are one such class of intelligent or smart material. They have been widely used in applications such as controlled drug release because of their biocompatibility with the human body and also because they resemble natural living tissue more than any other class of synthetic biomaterial. This is due to their

high water content and soft consistency that is similar to natural tissue [2–6]. Nguyen and West [7] presented a review on UV curable hydrogels that may be used as biomaterials in medical applications. Photopolymerisation is currently being used for an increased number of biomedical applications due to its ability to rapidly convert liquid monomer into a crosslinked network and also because no organic solvents are involved during the polymerisation process [8]. Hydrogels are becoming increasingly important materials for pharmaceutical applications. They are used in a variety of applications including diagnostic, therapeutic, and implantable devices, particularly in controlled release drug delivery systems, where they have been studied extensively [2, 4–6, 9–14].

Chemical crosslinking is a highly versatile method of creating hydrogels with good mechanical stability, which may be used in drug delivery applications [11, 12]. Thermosensitive hydrogels can be classified as positive or negative temperature-sensitive systems. A positive temperature-sensitive hydrogel has an upper critical solution temperature (UCST). Such hydrogels contract upon cooling below the UCST. Most hydrogels belong to this category. Negative temperature-sensitive hydrogels have a lower critical solution temperature (LCST). These hydrogels contract upon heating above the LCST, and are known as thermoreversible hydrogels as the phenomenon is totally reversible upon cooling [6]. Poly (*N*-isopropylacrylamide) (PNIPAAm) is the most popular of the temperature sensitive hydrogels, with its water solutions and hydrogels exhibiting a LCST at 32 °C [15–20]. The ability of PNIPAAm and its copolymers to be hydrophilic below the LCST and hydrophobic above the LCST has attracted many researchers [21–26]. Generally, in the case of temperature sensitive polymers, incorporation of a hydrophilic comonomer leads to an increase in LCST, whereas incorporation of a hydrophobic comonomer leads to a decrease [23, 24]. Poly (1-vinyl-2-pyrrolidinone) (PVP) is one such hydrophilic hydrogel, which is also sensitive to changes in temperature, non-toxic and is of particular interest to research due to its affinity to water [27].

Data reported in the literature on the mechanical properties of hydrogels are mostly obtained in tension/compression or using dynamic mechanical analysis. Dynamic mechanical methods have been successfully used to characterise the thermo/rheological properties of gel systems for polymeric films, for solid dosage coatings and as wound dressings [28, 29]. The mechanical properties of hydrogels are very important for pharmaceutical applications. For example, the integrity of the drug device during the lifetime of the application is very important to obtain 'food and drugs authority' (FDA) approval, unless the device is designed as a biodegradable system. A drug delivery system designed to protect a sensitive therapeutic agent, such as a protein, must maintain its integrity to be able to protect the protein until it is released out of the system [6]. Changing the degree of crosslinking has been utilised to achieve the desired mechanical property of the hydrogel. Increasing the degree of crosslinking of the system will result in a stronger gel [30]. However, a higher degree of crosslinking creates a more brittle structure. Hence, there is an optimum degree of crosslinking to achieve a relatively strong and yet elastic hydrogel. Copolymerisation has also being utilised to achieve the desired mechanical properties of hydrogels. Incorporating a comonomer that will contribute to hydrogen bonding can increase the strength of the hydrogel [6].

Of particular interest to the present investigation is the negative temperature sensitive properties of these hydrogels, which offers great possibilities for use in drug carrier systems. This study focuses on the thermal properties of random copolymers of NIPAAm and NVP over a range of temperatures investigating the effect that the temperature and the NVP content has on the LCST of the copolymer. Crosslinking agents of various molecular weights were incorporated to improve the usefulness of these hydrogels. Swelling studies were performed to determine the uptake of water and deswelling properties, while parallel plate rheometry was carried out to investigate the comparative strength of these hydrogels.

Experimental

Synthesis of polymers

The hydrogels investigated in this work were prepared by free-radical photopolymerisation. The monomers used were 1-vinyl-2-pyrrolidinone (NVP, Lancaster synthesis) and poly (*N*-isopropylacrylamide) (NIPAAm, TCI Europe). These polymers were crosslinked using ethylene glycol dimethacrylate (EGDMA) and poly(ethylene glycol) dimethacrylate with molecular weights 600 (PEG600DMA) and 1000 (PEG1000DMA) (All Sigma Aldrich) at 0.1 wt% of the total monomer content. The numbers 600 and 1,000 refer to the molecular weight of the poly(ethylene glycol) chain between the methacrylate groups. Both monomers and crosslinking agent were used as received. To initiate the reactions, 1-hydroxycyclohexylphenylketone (Irgacure® 184, Ciba speciality chemicals) was used as a UV-light sensitive initiator at 3 wt% of the total monomer weight. This was added to NVP/NIPAAm monomeric mixtures containing appropriate amounts of distilled water and stirred continuously until completely dissolved. The solution was then pipetted into a silicone mould (W.P. Notcutt, Middlesex) that contained disk impressions for swelling studies and rectangular impressions for use in

Fourier transform infrared spectroscopy (FTIR). The mould was positioned horizontally to the gravity direction under two UVA 340 UV lamps (Q-panel products) and the solution was cured for up to 6 h in an enclosed environment at ambient temperature. The samples were finally dried in a vacuum oven at 40 °C, 500 mmHg for at least 24 h prior to use and the composition of the hydrogels synthesised is listed in Table 1. The preparation of the linear copolymers is similar to that of the crosslinked copolymers as described above, but in the absence of crosslinker.

Fourier transform infrared spectroscopy

Fourier transform infrared spectroscopy was carried out on the rectangular samples that had being exposed to atmospheric conditions for a minimum of 7 days, using a Nicolet Avator 360 FTIR, with a 32 scan per sample cycle.

Phase transition determination

The DSC method was used for examination of the phase transition phenomenon exhibited by these thermosensitive gels. The analyses were preformed using a DSC 2920 Modulated DSC (TA Instruments) containing a refrigerator cooling system. The chemically crosslinked hydrogels were pre-equilibrated in distilled water at room temperature before testing. Homogeneous solutions of the physically crosslinked gels were prepared, by weighing appropriate amounts of the xerogel and distilled water, leaving these mixtures at room temperature for a period of hours/days. Samples of between 8 and 10 mg were weighed out using a Sartorius scales capable of being read to five decimal places. Aluminium pans were crimped before testing, with an empty crimped aluminium pan being used as the reference cell. Calorimetry scans were carried out from 20 to 55 °C for each of the copolymers. All DSC measurements were carried out at a scanning rate of 1 °C/min under nitrogen atmosphere. Calibration was preformed using indium as standard.

Table 1 Name and composition of hydrogels containing NVP, NIPAAm and distilled water in their monomeric feed ratio

Hydrogel name	NVP (wt%)	NIPAAm (wt%)	Distilled water (wt%)
A1(L1)	15	65	20
A2	15	60	25
A3	15	55	30
A4(L2)	20	65	15
A5	20	60	20
A6	20	55	25
A7	25	55	20
A8(L3)	30	60	10

Swelling kinetics

The swelling characteristics of the hydrogels were investigated in triplicate at ambient temperature. Samples of the cured polymer with an average mass of 1.086 g were placed into a petri dish. The petri dish was then filled with distilled water, the petri dish lid was put in place to prevent any evaporation and the gels were allowed to swell. Periodically, excess distilled water solution was removed after appropriate time intervals by pouring the solution through a Buchner funnel. The samples were then blotted free of surface water with filter paper, and the wet weight of the gel sample was measured at room temperature, using a Sartorius scales. The samples were resubmerged in fresh distilled water and the petri dish lid was replaced. Because measuring the weight of a swelling hydrogel is much easier than measuring the volume, the swelling ratio of hydrogels is usually expressed based on weights. Both the swelling ratio (R) and the 'water uptake' (W_u) of the hydrogels were calculated using the formulas:

$$R\,(\%) = \frac{W_t}{W_o} \times 100 \tag{1}$$

$$W_u\,(\%) = 100 \times \frac{(W_t - W_o)}{(W_e - W_o)} \tag{2}$$

where W_t is the weight of the swollen hydrogel after a given time period, W_o is the weight of the hydrogel before swelling experiments took place and W_e is the weight of the hydrogel at swelling equilibrium after 120 h [1, 2]. In order to provide a clear pictorial demonstration of the swelling behaviour of the gels and for comparative reasons, pictures of the swollen samples were taken after removal of the distilled water solution. All pictures were taken using a Fujifilm FinePix A310 digital camera with 3.1 mega pixels.

Kinetic deswelling

Hydrogel samples were allowed to reach equilibrium in distilled water at ambient temperature, as described previously. The equilibrated hydrogels were transferred into petri dishes containing distilled water at temperatures of 37 and 60 °C. At predetermined time intervals, the samples were removed from the water, excess polymer solution was removed by pouring the solution through a Buchner funnel, the surface was wiped with wet filter

paper and the hydrogel weighed. Water retention (W_r) was defined as:

$$W_r\,(\%) = 100 \times \frac{(W_t - W_o)}{(W_e - W_o)} \quad (3)$$

where the symbols are the same as defined in section ''Swelling kinetics''. This process was continued for approximately 72 h at which point the samples were removed from the distilled water solution, weighed and dried in a vacuum oven at 80 °C for 24 h.

Reswelling kinetics and gel fraction measurement

On removal from the vacuum oven, the xerogels were again immersed in distilled water and allowed reswell at ambient temperature, following the same procedure as the original swelling. Both the swelling ratio (R) and the 'water uptake' (W_u) of the hydrogels were calculated using the formulas, as described previously. The gel fraction was determined using samples, which had been swollen in distilled water for several days to a constant weight (equilibrium swelling) in order to remove the soluble parts. The gels were then deswelled in water at 60 °C and dried in a vacuum oven at 80 °C for 24 h. The gelation% was calculated by the following equation:

$$\text{Gelation}\% = \frac{W_{ex}}{W_o} \times 100 \quad (4)$$

where W_o and W_{ex} are the weight of the dried gel after photopolymerisation, and the dried weight of the sample after extraction of soluble parts, respectively.

Effect of LCST on elasticity

Rheological measurements were performed using an ''Advanced Rheometer AR1000'' (TA instruments) fitted with a Peltier temperature control. The geometry used was a 6 cm diameter parallel steel plate with a roughened surface to minimise slippage. The temperature was ramped from 20 to 80 °C with tests carried out at a ramp rate of 2 °C/min. The tests were in oscillation mode at frequencies of 1, 5.5, and 10 Hz, using a constant strain, γ, of 10%. In all experiments, a weak normal force was applied to the surface of the sample discs in order to avoid the sweeping of the gel from the tool plates. This force resulted in a slight compression of the sample. All rheological measurements were carried out on samples that had been synthesised using different molecular weight crosslinking agents, and allowed to swell at room temperature for 120 h.

Comparative strength of the hydrogels

Parallel plate rheometry was carried out on samples, which had been synthesised with different molecular weight crosslinking agents, using an ''Advanced Rheometer AR1000'' (TA instruments) fitted with a Peltier temperature control. These samples had previously been swelled in distilled water for at least 120 h. The samples were tested using a 6 cm steel plate with a roughened surface to minimise slippage. The swollen hydrogels were placed on the Peltier plate at 20 °C, and tests carried out using a strain sweep from 1 × E-4 to 1 at a frequency of 1 Hz. A constant ''normal force'' of 5 ± 0.5 N exerted on the samples, to determine the point at which the sample's interactions were increasingly stretched until they are broken. This resulted in a drop in the elastic component G', and thus there was a crossing of G' and G''.

Results and discussion

Preparation of samples

Polymerisation of water-soluble monomers in the presence of crosslinking agents leads to the formation of chemically crosslinked hydrogels. Most biomedical hydrogels are synthesised by free radical polymerisation [31]. Exposure to the UV-light source produces free radicals by decomposition of the photoinitiator, which initiates polymerisation of the monomers [7]. In this work, chemically crosslinked samples of NVP/NIPAAm were photopolymerised in the presence of small amounts of distilled water, using Irgacure® 184 as a photoinitiator. Initiating polymerisation by radiation curing is beneficial as it reduces the need for volatile organic solvents, and allows temporal control of initiation and is also more rapid than thermal polymerisation. However, it is difficult and expensive to undertake photopolymerisation in an environment free of molecular oxygen, a well-known inhibitor of free radical polymerisation. To this end, polymer scientists have often included NVP in photopolymer formulations as it has been shown to dramatically reduce oxygen inhibition [32]. It was found that NIPAAm monomer could be dissolved more readily in aqueous solutions of NVP, than in pure liquid NVP alone. This allowed greater freedom in LCST control when compared with hydrogels prepared in the absence of distilled water [26]. In general, as the polymer chain contains more hydrophilic constituent, the LCST becomes higher [23, 24]. By alternating the feed ratio, using the hydrophobic NIPAAm monomer and hydrophilic NVP monomer, copolymers were synthesised to have their own distinctive phase transition temperatures. This ability to shift the LCST of these thermosensitive hydrogels provides excellent

flexibility in tailoring transitions for specific uses. From visual inspection of these samples, there was no significant difference between the linear copolymers and the crosslinked copolymers, which were transparent and glass like in appearance after the photopolymerisation process.

Fourier transform infrared spectroscopy

PVP/PNIPAAm copolymers were characterised using FTIR. NVP and NIPAAm monomers were initially investigated using this technique. Two very strong bands were observed for pure liquid NVP in the IR spectrum; the first a C=C bond stretching vibration at 1,623 cm^{-1}, corresponding to olefinic (C=C) stretching, while the second band, due to carbonyl stretching (C=O) is located at 1,700 cm^{-1}. Strong peaks in the range 800–1,000 cm^{-1} corresponding to the stretching mode of vinyl double bonds were also recorded. Similar findings have been reported by Száraz and Forsling [33] and Sun [34]. Characteristic peaks of NIPAAm monomer were found at 1,618 cm^{-1} (C=C), at 1,407 cm^{-1} (CH_2=) and between 986–913 cm^{-1} for the vinyl group peaks. This is in agreement with work carried out by Kim et al [25] and Ju et al. [35]. The disappearance of the characteristic NVP and NIPAAm monomer peaks in the PVP/PNIPAAm copolymer spectra indicate that the polymerisation reaction has taken place. Characteristic peaks for the synthesised copolymers were observed at 1,641 cm^{-1} for C=O, at 1,538–1,540 cm^{-1} for NH, and at 1,386 and 1,366 cm^{-1} representing the isopropyl group. These values are in good agreement with work carried out by other authors [22, 23, 35]. The FTIR spectrum of physically crosslinked A1(L1) xerogel is shown in Fig. 1. The addition of the crosslinking agent to the monomeric mixture of samples A1(L1) and A4(L2) was found to have little affect on the characteristic peaks of the xerogels.

Phase transition determination

The primary objective of this work was to produce hydrogels with a LCST in the region of 37 °C. As already discussed, aqueous PNIPAAm water solutions and hydrogels have a phase transition temperature of about 32 °C [15–20], which may be determined using DSC analysis, giving an endothermic transition peak. Modulated DSC has been compared with conventional DSC in phase transition determination of physically crosslinked gels, in a previous study [26]. Modulated DSC provides information about the reversing (heat capacity component of the total heat flow) and non-reversing (kinetic component of the total heat flow) characteristics of thermal events. As the phase transition temperature is a totally reversible transition [18, 20], this behaviour was examined using the heat capacity component. The findings showed that the reversing heat flow signal yielded a much more defined endotherm than the other signals and provided much greater sensitivity in LCST determination, when compared with conventional DSC. In literature to date, it is important to note that authors have differed in their interpretation of the phase transition endotherm. Otake et al. [20] defines the phase transition temperature as the onset of the transition endotherm (the interaction of the baseline and the leading edge of the endotherm), while Schild et al. [36] defines it as the temperature at the peak of the thermogram. This should always be taken into consideration, when analysing transition temperatures by calorimetry as peak and onset values may differ by a

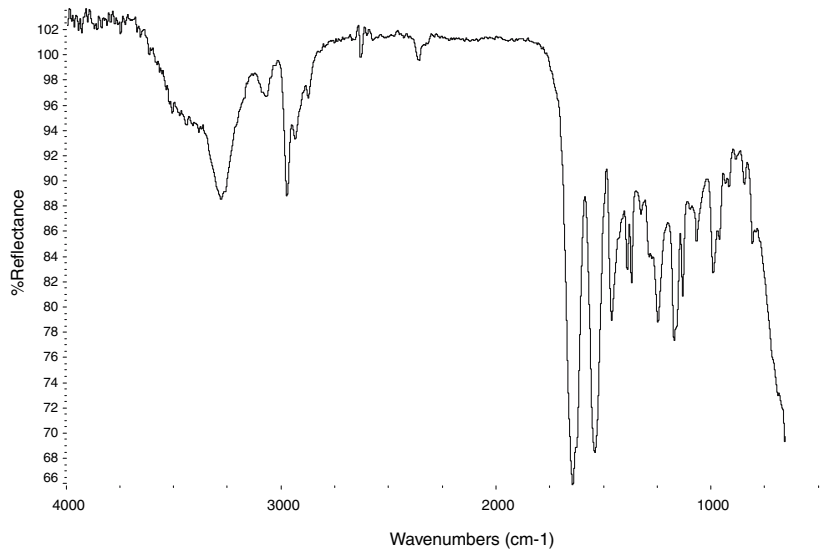

Fig. 1 FTIR spectrum of physically crosslinked hydrogel A1(L1)

number of Degrees Celsius. In this work, both peak onset and peak maximum values were recorded.

The LCST of the thermosensitive gels was controlled by adjusting the relative hydrophobicity. This was achieved by copolymerising hydrophobic NIPAAm monomer with hydrophilic NVP monomer at varying feed ratios. NVP has the effect of raising LCST, and the effect becomes more pronounced with increasing NVP content. The percentage NVP monomer was calculated with respect to NIPAAm monomer incorporated in the initial feed ratio and an almost linear increase in phase transition temperature was observed with increasing hydrophilic component, as represented for 3 wt% PNIPAAm/PVP aqueous copolymer solutions in Fig. 2. In this work, there is a difference of over 2 °C between calorimetric onset and peak maximum values. It is believed that a small fraction of the gel begins to undergo its phase transition at the onset temperature, while the bulk undergoes the transition at the peak maximum value. Hydrogels A1(L1) and A4(L2) were chosen for further investigation as they both have phase transition temperatures near body temperature, which is important especially for drug delivery applications. A1(L1) has a LCST onset value of 36.80 °C and a peak maximum value of 38.90 °C, while A4(L2) has onset value of 38.90 °C and peak maximum value of 40.80 °C, as illustrated in Fig. 3. The relatively strong hydrogen bonds formed between water molecules and N–H or C=O groups in dilute solutions, become weaker and break as temperature is raised, resulting in the endothermic heat of phase separation.

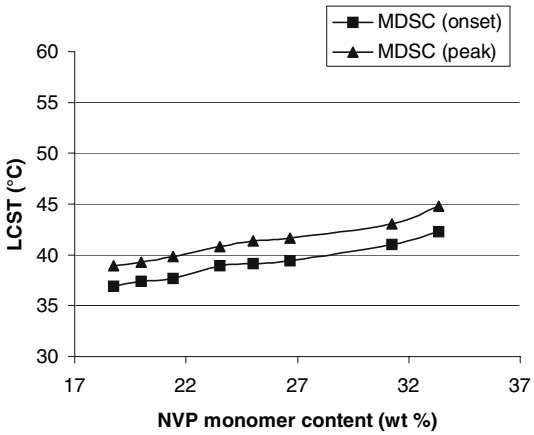

Fig. 2 Onset and peak maximum LCST values of 3 wt% PNIPAAm/PVP aqueous copolymer solutions with increasing NVP monomer content, established using Modulated DSC

Eeckman et al. [24, 37, 38] suggests that copolymers of PNIPAAm should have a sharpness of phase transition comparable to that of the homopolymer. Both A1(L1) and A4(L2) are not quite as symmetrical as PNIPAAm homopolymer [26] and are characterised by a sharp leading edge followed by a gradually declining tail. The relatively large breadth of the endotherms, which is also observed for the crosslinked samples, is probably related to the specific thermosensitive properties of these polymers. In general crosslinked polymers (for which thermosensitive properties are reflected in their swelling characteristics) exhibiting gradual deswelling with increasing temperature show broad endothermic peaks, while crosslinked polymers exhibiting sharp deswelling at their LCST show narrow endothermic peaks [19]. All aqueous copolymer solutions were made up at 3 wt%, as it is important to keep polymer concentration constant, as the transition enthalpy (ΔH) has been found to be concentration dependent [18, 19]. The heat of phase transition was found to be 0.5945 J/g for aqueous PNIPAAm solution [26] and 0.3604 and 0.2296 J/g for A1(L1) and A4(L2), respectively. Feil et al. [19] suggests that a

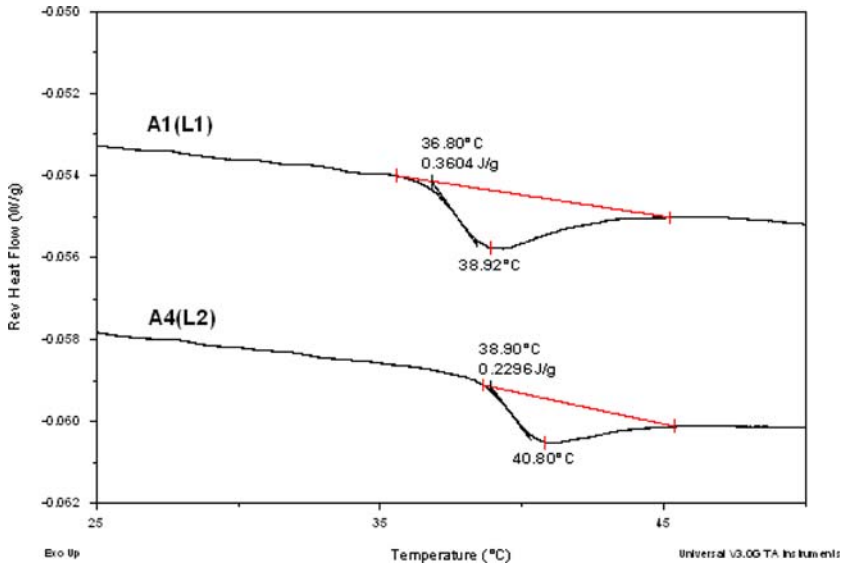

Fig. 3 Onset and peak maximum LCST values of 3 wt% A1(L1) and A4(L2) aqueous copolymer solutions, established using Modulated DSC

higher LCST leads to a reduced heat of phase separation due to the smaller amount of structured water at higher temperatures. This behaviour was observed for both hydrogels and linear solutions.

The temperature that induces gel collapse corresponds to the LCST of the uncrosslinked polymer [39], and both onset and peak maximum values were again recorded for the crosslinked samples. The transition temperature of linear polymer samples is independent of molecular weight [20]. Thus, it is expected to be the same as the transition temperature of the chemically crosslinked hydrogels. Schild [39] states that the two transition temperatures, however, may vary slightly depending on the nature of the crosslinking agent. The hydrogels in this work were crosslinked using EGDMA, PEG600DMA and PEG1000DMA. For each of the samples tested, use of the chemical crosslinking agent was seen to reduce the phase transition temperature by a number of degrees Celsius, when compared with the linear polymers. However, the variation in molecular weight of the crosslinking agent had little effect on the transition temperature of the hydrogels. There is a decrease of approximately 3 °C (onset value) and 2 °C (peak value) in phase transition temperature for each of the molecular weight crosslinkers incorporated in hydrogel A1(L1) when compared with the physically crosslinked samples, as can be seen in Fig. 4. A reduction in transition enthalpy is noted for the hydrogels when compared with the linear gels. Other authors have made similar observations for aqueous PNIPAAm solutions and hydrogels [19, 20]. Hydrogel A4(L2) exhibited similar trends as A1(L1), with a decrease in onset and peak maximum transition temperature values with incorporation of each of the chemical crosslinking agents. The molecular weight of the crosslinker was once more found to have no notable effect on the phase transition temperature and a decrease in the transition enthalpy was again observed when compared with the physically crosslinked sample.

Swelling studies

Physically crosslinked hydrogels

Swelling experiments were performed on circular discs of photopolymerised polymer in distilled water, at temperatures ranging from ambient temperature to 40 °C, for the physically crosslinked gels. This covers the range of phase transition temperatures of the gels, as determined by modulated DSC. In physically crosslinked gels, dissolution is prevented by physical interactions, which exist between the polymer chains. Narasimhan and Peppas [40] states that when an uncrosslinked, amorphous, glassy polymer is brought into contact with a thermodynamically compatible solvent, the latter dissociates into the polymer, and when the solvent concentration in the swollen polymer reaches a critical value, chain displacement begins to dominate and the polymer is eventually dissolved. With increasing temperature, a reduction in dissolution time is also noted. This is a common property of most physically crosslinked polymers, as they increase their water-solubility as the temperature increases.

The negative temperature sensitive gels synthesised in this work exhibit a LCST in aqueous media, below which they are water soluble and above which they become slightly less water soluble; or significantly less water soluble; depending on the composition of the gel. Hydrogel A1(L1) clearly displayed inverse temperature solubility. Onset and peak maximum phase transition temperatures were recorded at 36.93 and 38.92 °C, respectively using

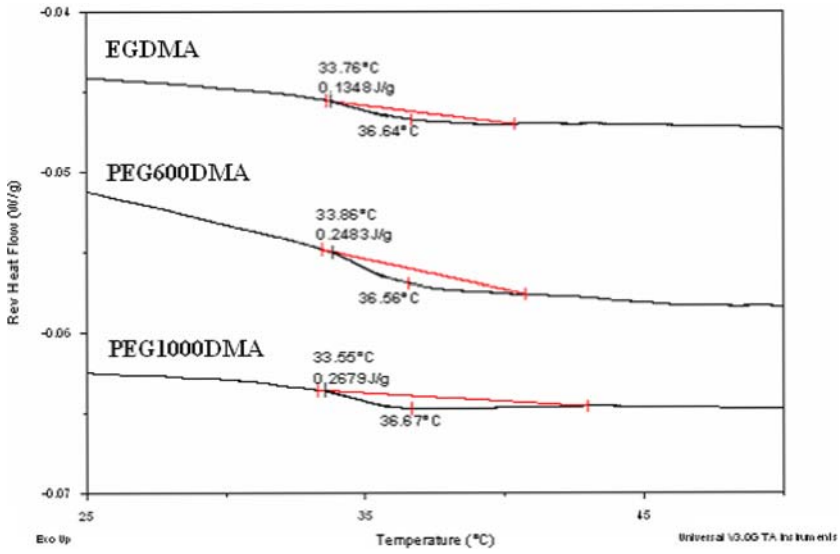

Fig. 4 Onset and peak maximum LCST values of chemically crosslinked A1(L1) synthesised using different molecular weight crosslinking agents, established using Modulated DSC

modulated DSC. The gel reached its maximum swollen weight between 24 and 48 h at each of the swelling temperatures used. At room temperature and 35 °C, which are below the LCST of the gel, the dissolution phase is complete within 96 h. At 37 °C, the hydrogel takes another 24 h to dissolute. At 40 °C, which is above the transition temperature established by MDSC, the samples had still not dissolved after 120 h. Similar temperature sensitive swelling behaviour was observed for gel A4 (L2) [2, 26]. In practice, to achieve high degrees of swelling, it is common to use synthetic polymers that are water-soluble when in non-crosslinked form.

Chemically crosslinked hydrogels

Swelling kinetics. When the hydrogels are covalently crosslinked, they will not dissolve in water irrespective of changes in temperature. Instead, they will undergo dramatic changes in the extent of swelling. The chemically crosslinked hydrogels were allowed to equilibrate in distilled water at room temperature. When immersed in distilled water, the UV cured glassy matrices swelled to become soft and flexible. A hydrogel swells for the same reason that an analogous linear polymer dissolves in water to form an ordinary polymer solution [40]. The crosslinked samples were compared with the uncrosslinked polymers and it was found that a much higher degree of swelling was achieved for the crosslinked samples, as represented in Fig. 5. This was due to the chemical crosslinks preventing dissolution and hence an apparent higher degree of swelling was observed. For example, when swollen in distilled water for 48 h at room temperature, uncrosslinked A1(L1) had a swelling ratio of 464%, while the crosslinked samples that contained EGDMA, PEG600DMA and PEG1000DMA yielded values of 1,471, 1,611 and 1614%, respectively.

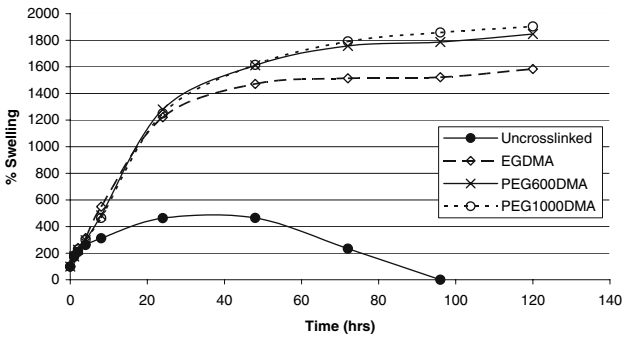

Fig. 5 Percentage swelling behaviour at room temperature of physically and chemically crosslinked hydrogel A1(L1) (chemically crosslinked samples were synthesised using different molecular weight crosslinking agents)

Panayiotou and Freitag [41] carried out work on the effect of crosslinking degree on the swelling behaviour of PNIPAAm hydrogels and concluded that a lower degree of crosslinking leads to a higher swelling ratio. As the crosslinking agent incorporated in this study was 0.1 wt% of the total monomer content in all instances, the number of crosslinking chains per mass of liquid decreases as the molecular weight of the crosslinking agent increases. This led to high swelling values, which increased with increasing molecular weight of the crosslinking agent, as depicted in Fig. 5. The samples containing higher molecular weight crosslinking agents swelled to a higher extent by virtue of their longer crosslinked chain lengths. Swelling in all cases was found to change the size of the original hydrogel, while the original shape was maintained. If a xerogel imbibes at least 20 times its own weight of aqueous fluid while retaining its original shape, it is called a superabsorbent hydrogel [39]. The samples synthesised with the higher molecular weight crosslinking agents absorbed over 18 times their weight in water, while maintaining good gel integrity but cannot be characterised as superabsorbent. The typical swelling behaviour of the hydrogels at room temperature can be clearly seen in Fig. 6.

Figure 7 shows the dependence of water uptake on molecular weight of the crosslinking agent, for hydrogel A1(L1). At the first stage of the curve, the swelling rate is very high, and the water can penetrate easily into the polymer network. This is highlighted by the fact that after 24 h, water uptake is over 50% of the total water absorption of the fully hydrated hydrogels, for each of the molecular weight crosslinking agents used. As the test samples approached complete hydration, the rate of water absorption began to level off. This is due to the retractive force of the crosslinked structure counterbalancing the thermodynamically driven swelling [6]. Between 0 and 72 h, it would appear that hydrogels containing lower molecular weight crosslinking agents yielded a more rapid rate of water uptake. However, it should be taken in to consideration that this value is representative of the overall water uptake and that the higher the molecular weight of the crosslinking agent, the more water the hydrogel could imbibe (see also Fig. 5). This behaviour was found for both monomeric concentrations, as the polymers were observed to swell to a higher degree as the molecular weight of the crosslinking agents increased.

Deswelling kinetics. Zhang et al. states that the temperature dependence of the swelling ratio only demonstrates the equilibrium swelling hydration state of responsive gels at different temperatures. In practical applications, the temperature response kinetics or deswelling (shrinking) kinetics of hydrogels upon the suddenly altered stimulation, such as temperature changes, is more important [42]. Each of the negative temperature sensitive hydrogels studied

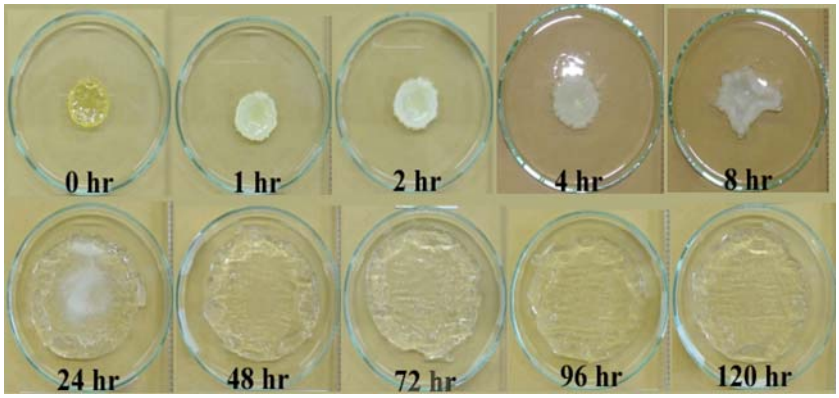

Fig. 6 Typical swelling of hydrogel A1(L1) crosslinked with PEG1000DMA crosslinking agent, at room temperature. All of the hydrogels showed similar swelling behaviour at room temperature

tended to shrink and lost water once immersed in hot water. Figures 8 and 9 present the shrinking kinetics of thermosensitive hydrogel A1(L1), after transferring equilibrium swollen hydrogel samples at room temperature (below their volume phase transition temperature) to distilled water at 37 °C (approximate MDSC peak maximum value of A1(L1) using each molecular weight crosslinking agent) and 60 °C (over 20 °C above their transition temperature), respectively. The deswelling experiments were conducted at 37 °C in order to simulate the use of the hydrogel at body temperature, as chemically crosslinked hydrogels have been extensively investigated for use in release of pharmaceutical agents [4–6, 12, 24], and commercially used as dressings in wound healing applications [43].

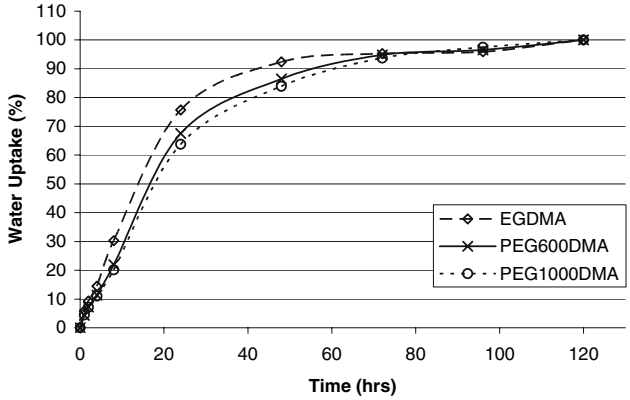

Fig. 7 Effect of molecular weight crosslinking agent on the swelling kinetics of hydrogel A1(L1) at room temperature

Each of the samples showed similar deswelling behaviour at 37 °C, as fast release for the first 24 h was followed by a much slower rate of water desorption. This feature could be particularly beneficial in controlled drug release applications, where an initial burst release followed by a period of sustained release is often advantageous [4, 6]. The molecular weight of crosslinking agent was found to have an effect on the deswelling behaviour, at 37 and 60 °C. In both cases, an increase in the molecular weight of the crosslinking agent used, the faster the shrinking rate of the hydrogel. This is due to the longer crosslinked chains allowing water to escape more rapidly. The relatively broad endothermic peaks established by modulated DSC for each of our thermosensitive hydrogels correspond to gradual deswelling with increasing temperature, in agreement with work carried out by Feil et al. [19]. At the higher deswelling temperature of 60 °C, it still takes our

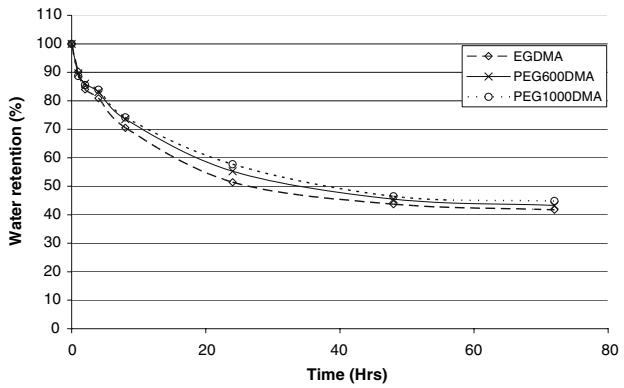

Fig. 8 Effect of molecular weight crosslinking agent on the deswelling kinetics of hydrogel A1(L1) at 37 °C

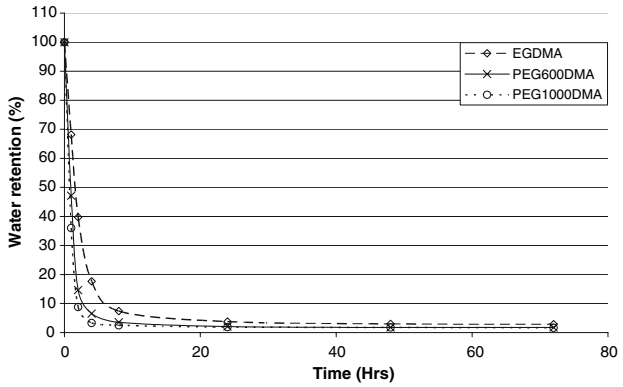

Fig. 9 Effect of molecular weight crosslinking agent on the deswelling kinetics of hydrogel A1(L1) at 60 °C

hydrogels between 2 and 8 h (depending on the molecular weight of the crosslinking agent) to release over 90% of their water content. Hydrogels have been produced, which can release over 90% of the their water content within 10 min, under similar deswelling conditions [42], and would exhibit narrower endothermic peaks.

During the shrinking process, at the higher deswelling temperature, a thick dense white skin layer was formed and bubbles appeared on the surface of the hydrogels, as can be seen in Fig. 10. Zhang et al. found similar behaviour for PNIPAAm homopolymer, and believed the hydrogel to be impermeable to the inner water, once the skin layer was formed. He concluded that once this skin layer is formed, the freed inner water molecules are prevented from diffusing out and that blowing up some parts of the dense skin layer compensates this increasing inner pressure thus, bubbles appear on the surface of the hydrogel [44]. However, when our hydrogels were deswelled at 60 °C, they released almost all imbibed water, despite displaying a thick skin layer and distinctive bubbles almost immediately after been placed in distilled water, at the deswelling temperature. It is hypothesised that the introduction of the hydrophilic component in the copolymerisation results in a more permeable skin layer, which allows the water to be released during the deswelling process. These behaviours were not evident for the hydrogels deswelled at 37 °C, although a less distinctive skin layer was noted; no bubbles were formed during the deswelling process. This is because the deswelling temperature is only marginally higher than the volume phase transition temperature of these hydrogels, so the hydrophobic interactions may not have become as dominant.

The hydrophilic and hydrophobic balance of polymer side groups in PNIPAAm hydrogels, i.e., –CONH– is hydrophilic and $–CH(CH_3)_2–$ is hydrophobic [19, 42], are responsible for this interesting swelling and deswelling behaviour. In the hydrophilic region, the water molecules are connected with the side chains by hydrogen bonds between the water molecules and hydrophilic groups. These hydrogen bonds act cooperatively to form a stable hydration shell around the hydrophobic groups [42]. Because of the hydrophilic nature of polymer chains, the hydrogels absorb water to swell in the presence of abundant water. Above phase transition temperature, these interactions are destroyed and as a result the entrapped water molecules are released. After deswelling for 72 h, the samples were removed from the distilled water solution, weighed and dried in a vacuum oven for 24 h, prior to further use.

Reswelling kinetics and gel fraction measurement. On removal from the vacuum oven, the xerogels were immersed in distilled water at ambient temperature and allowed to reswell, following the same procedure as that of the original swelling. A similar trend is again observed, as the hydrogels synthesised with the higher molecular weight crosslinking agent swelled to a higher degree, as can be seen in Fig. 11. One notable difference between the reswelled hydrogels and those swollen in the original swelling cycle is an increase in the swelling ratio. However, this is attributed to the removal of any soluble parts caused by the original swelling and deswelling process, resulting in a decreased W_o value, and so apparent higher percentage swelling values. The molecular weight of the crosslinking agent did not appear to have any obvious effect on the gel fraction, with values of approximately 75%, for hydrogel A1(L1) and A4(L2) using EGDMA, PEG600DMA and PEG1000DMA.

Rheometry

A variety of methods have been used for the mechanical analysis of hydrogels. The most used involve elongation/compression analysis, dynamic mechanical analysis

Fig. 10 White skin layer and bubbles characteristic of all hydrogels, after deswelling at 60 °C for 1 h

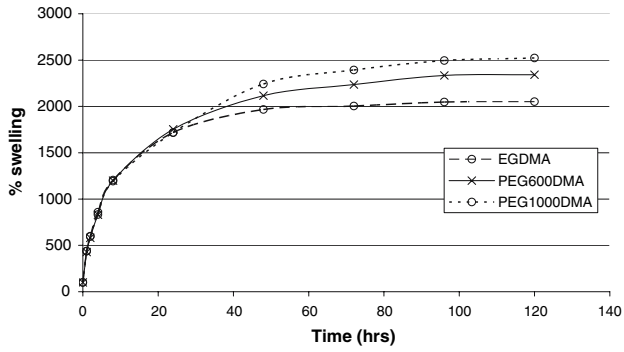

Fig. 11 Percentage reswelling behaviour of chemically crosslinked hydrogel A1(L1) at room temperature (chemically crosslinked samples synthesised using different molecular weight crosslinking agents)

(DMA) and oscillatory rheometry. These analyses provide information on the gel strength expressed as viscosity or elasticity and the relation of this strength with the gel composition and its stability [29]. To examine the stress–strain relationship for the hydrogels, they were subjected to an alternating strain, while simultaneously measuring the stress. For viscoelastic behaviour, when equilibrium is reached, the stress and strain will both vary sinusoidally, but the strain lags behind the stress. These relationships are shown in Eqs. 5 and 6 [45].

$$\text{Strain } e = e_o \sin \omega t \tag{5}$$

$$\text{Stress } \sigma = \sigma_o \sin(\omega t + \delta) \tag{6}$$

where ω is angular frequency and δ is the phase lag. The stress strain relationship can be defined by quantities G' and G'' which are 90° out of phase with the strain [45]. These are described in Eqs. 7 and 8.

$$G' = (\sigma_o/e_o)\cos\delta \tag{7}$$

$$G'' = (\sigma_o/e_o)\sin\delta \tag{8}$$

G' is in phase with the solid and is called the storage modulus because it defines the energy stored in the specimen due to the applied strain and G'' which is $\pi/2$ out of phase with the strain defines the dissipation of energy and is called the loss modulus [45]. It should be noted that for small strain amplitudes G' is independent of the strain amplitude. The following experiments were performed at the low strain amplitude which is the constant regime for G'.

Effect of LCST on elasticity

The typical rheological behaviour of negative temperature sensitive equilibrium-swollen hydrogels, synthesised with different molecular weight crosslinking agents, over a temperature range of 30–70 °C, is shown in Fig. 12. The hydrogels are viscoelastic solids with both the storage modulus and the loss modulus being temperature dependent [46]. The general trend that emerges from the results, is that G' is much larger than G'', over the temperature range of the test. This is because the elastic response dominates, which is typical for gels and solid like materials. Each of the frequencies resulted in a negligible variation in G'' values with increasing temperature, so the temperature dependent behaviour was studied using only G'. Below the volume phase transition temperature of the hydrogels there is little variation in the strength of each of the samples with increasing temperature. At a temperature corresponding approximately to the phase transition temperature, there is an increase in strength of the hydrogels, which becomes more dramatic with increasing temperature. This behaviour corresponds to the formation of a thick skin layer at temperatures above the transition temperature of the hydrogels, as found in deswelling experiments. This trend is in good agreement with the deswelling analysis, as a more distinctive skin layer is observed at higher deswelling temperatures, as discussed in section ''Deswelling kinetics''. At 70 °C, samples crosslinked with EGDMA are almost twice as strong as they were below their volume phase transition temperature, while hydrogels crosslinked with PEG1000DMA show an increase in strength six times that of their value below transition temperature, for each of the frequencies used.

While, the trends observed remain constant throughout testing, it was not possible to obtain a desired level of reproducibility and thus accurate quantitative results, using this procedure. This is due to the release of water (deswelling behaviour) from the hydrogels at temperatures above the volume phase transition temperature. As a result, it was not possible to keep a constant ''normal force'' on the hydrogels for the duration of the test and also, the amount of water dissipated above the phase transition temperature results in slippage, despite the use of the roughened parallel plate geometry. As a result, the comparative strength of the hydrogels was investigated at a temperature below the transition temperature, and is discussed in section ''Comparative strength of the hydrogels''. Nonetheless, the technique described is much preferred to qualitative assessment by observation and feeling, which is highly reliant on the experience of the person carrying out the test.

Comparative strength of the hydrogels

Parallel plate rheometry was carried out at 20 °C on swollen crosslinked gels to investigate the comparative strength of these hydrogels. Tests were conducted at 20 °C as above the volume phase transition temperature, the hydrogels release water, which would cause slippage and also it would be difficult to maintain a constant force on the hydrogel through the duration of the experiment. A strain sweep from 1 × E-4 to 1 at a frequency of 1 Hz, with a constant ''normal force'' of 5 ± 0.5 N exerted on the samples, was preformed to determine the point at which the hydrogel breaks down. This was the point at which the sample's interactions are increasingly stretched until they are broken and this results in a drop in the elastic component G', and thus there was a crossing of G' and G''.

The strength of the hydrogels shows obvious dependence on the molecular weight of the crosslinking agent, as shown in Fig. 13. The chemically crosslinked hydrogels yielded

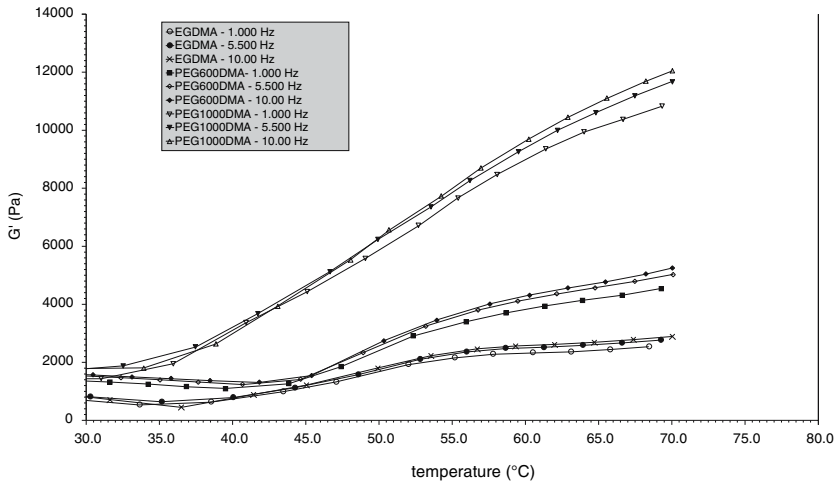

Fig. 12 Effect of temperature on storage modulus of hydrogel A1(L1) crosslinked with different molecular weight crosslinking agents

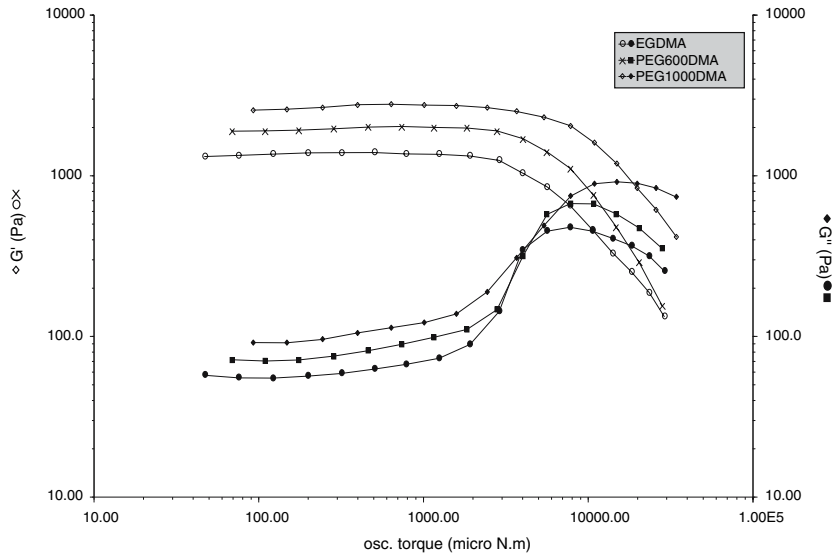

Fig. 13 Parallel plate rheometry of samples crosslinked with EGDMA, PEG600DMA and PEG1000DMA

constant G' values of approximately 1,300, 1,900 and 2,300 Pa, under an oscillating torque of up to 4,000 μN m, for EGDMA, PEG600DMA and PEG1000DMA, respectively. These values reflect favourable when compared with values quoted by Jones and Vaughan [43] who reviewed a variety of commercially available biomedical hydrogel wound dressings. The oscillating torque at break achieved by the polymers was also seen to increase as the molecular weight of the crosslinking agent increased. Oscillatory torque values of 10,995, 12,679, and 20,821 μN m were obtained for hydrogel A1(L1), which was crosslinked with EGDMA, PEG600DMA and PEG1000DMA, respectively. Hong et al. [47] stated that, at low concentrations of crosslinking agents, branched polymers are mainly formed. Even though low concentrations of crosslinking agents were used in this work, the polymer retained its shape and did not dissolve. This indicates that crosslinking did occur. However, it is probable that some branching did occur. The molecular length of these branches would increase with increasing molecular weight of the crosslinking agent, and therefore these longer branches could act as a 'tie' between molecular chains, and distribute any load more evenly. This would yield higher comparative gel strength. The longer molecular chains could also impart greater flexibility and a greater force would be required to break the polymer chains. These results indicate the feasibility of producing hydrogels of high mechanical strength, which are temperature sensitive.

Conclusion

We have synthesised a series of chemically crosslinked random copolymers, containing NVP and NIPAAm at different monomeric concentrations, by photopolymerisation. The FTIR spectra of PVP-PNIPAAm complexes indicate

that successful polymerisation of each of the monomers has taken place. The phase transition temperature of the gels was determined by calorimetry. By alternating the feed ratio, using the hydrophobic NIPAAm monomer and hydrophilic NVP monomer, copolymers were synthesised to have their own distinctive phase transition temperatures. The samples synthesised with higher molecular weight crosslinking agents absorbed over 18 times their weight in water, while maintaining good gel integrity, and so fall marginally short of being characterised as superabsorbent. Each of the negative temperature sensitive hydrogels studied tended to shrink and lost water once immersed in distilled water above their volume phase transition temperature. The deswelling experiments were conducted at 37 °C in order to simulate the use of the hydrogel at body temperature. Each of the samples showed similar deswelling behaviour at this temperature, as fast release for the first 24 h was followed by a much slower rate of water desorption. This feature could be particularly beneficial in controlled drug release applications, where an initial burst release followed by a period of sustained release is often advantageous. Rheological studies showed that by increasing the molecular weight of the crosslinking agent, an increase in gel strength could be achieved. This is more advantageous than increasing the degree of crosslinking to produce stronger hydrogels as they result in hydrogels that can imbibe less water.

In conclusion, we have produced hydrogels with high water uptake and relatively high mechanical strength, which are temperature sensitive and show potential for a variety of drug delivery applications. These could include oral drug delivery, drug eluting polymeric coatings or as dressings in wound healing applications. Further work has to be undertaken in order to investigate the effect of different pH buffer solutions on the phase transition temperature of the copolymers and the incorporation of a number of different drugs into the gels is to be carried out, as both have been known to significantly affect the LCST. By doing so, it is hoped to design drug-loaded gels that will release at a predicted rate in given media, as a function of temperature.

Acknowledgements This study was supported in parts by grants from both Enterprise Ireland and the Athlone Institute of Technology research and development fund.

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