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Photopolymerisation and characterisation of negative temperature sensitive hydrogels based on *N*,*N*-diethylacrylamide

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Abstract Despite the many advantages of photopolymerisation in the fabrication of hydrogels, studies on the synthesis of poly(*N*,*N*-diethylacrylamide) (PDEAAm) using this technique have received limited attention in the literature. A series of temperature sensitive hydrogels were prepared by free-radical crosslinking copolymerisation of *N*,*N*-diethylacrylamide (DEAAm) with 1-vinyl-2-pyrrolidinone (NVP) and *N*,*N*-dimethylacrylamide (DMAAm), respectively. Two ultraviolet (UV) light sensitive initiators were trialled in the synthesis, namely 1-hydroxycyclohexylphenylketone and 2-hydroxy-1-[4-(hydroxyethoxy)phenyl]-2-methyl-1-propanone, with poly(ethylene glycol)dimethacrylate being used as the crosslinking agent. The lower critical solution temperatures (LCSTs) of the hydrogels synthesised were shown to be close to body temperature using cloud point measurement and modulated differential scanning calorimetry, which is favourable particularly for 'smart' drug delivery applications. The swelling behaviour of the samples was investigated upon stepwise temperature change revealing that the hydrogels underwent reproducible pulsatile swelling behaviour. Oscillatory rheological studies showed that increasing the ratio of crosslinking agent could be used as a means of improving the mechanical properties of the photopolymerised temperature sensitive hydrogels.

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Introduction

The development of novel drug delivery systems is an extremely active area of the biomedical industry, and there are obvious economic and therapeutic advantages to improving the manner in which drugs are administered [1]. One major challenge is the controlled delivery of therapeutic agents in a pulsatile or staggered fashion [2]. Ideally, it would be most desirable if the drug(s) could be administered in a manner that precisely matched physiological needs at appropriate times (temporal modulation) and/or at the appropriate site (site-specific targeting) [3]. Hydrogels, and more specifically environment-sensitive smart hydrogels, have become the materials of choice when designing such drug delivery systems. The most widely studied smart hydrogels are those with either temperature or pH sensitivity.

The most commonly used negative temperature sensitive hydrogels, including poly(*N*-isopropylacrylamide) (PNIPAAm), display weaknesses that have limited clinical applications [3, 4]. It would clearly be easier to win approval for responsive gels made from polymers that already had some approved status. Unfortunately, however, such polymers on the FDA's 'generally recognised as safe' list are limited by high LCSTs, which renders them unsatisfactory for temperature-responsive drug delivery [4]. Therefore, extensive toxicity studies are required before clinical applications can emerge [3]. Poly(*N*,*N*-diethylacrylamide) (PDEAAm) thermoresponsive linear polymers have lower critical solution temperatures of approximately 32 °C, similar to that of PNIPAAm homopolymer [5–9]. PDEAAm is, however, considered more suited to applications in the life sciences, than PNIPAAm. When compared, it was concluded that cytotoxicity was more pronounced for PNIPAAm samples, than for PDEAAm samples similarly prepared [9–11].

Initiating polymerisation by radiation curing is beneficial as it reduces the need for volatile organic solvents, allows temporal control of initiation and is also more rapid than thermal polymerisation. Rapid curing is also achievable with Irgacure 184 and of 19 photoinitiators analysed by Segurola et al. [12] it exhibited the best results with regards to minimal discolouration (yellowing) during photocure. Williams et al. [13] investigated the variable cytocompatibility of a number of photoinitiators including Irgacure 184 and Irgacure 2959 and concluded that the latter was well tolerated by many cell types over a range of mammalian species (photoinitiators were not exposed to UV light prior to analysis). Also, Irgacure 2959 does not produce benzaldehyde upon exposure to UV light, therefore, cured films have low odour. Photopolymers previously synthesised using Irgacure 184 have been reported to have potential for biomedical applications [14], while Irgacure 2959 is frequently used in tissue engineering research [15, 16].

Our research group has previously reported on the photopolymerisation of temperature and pH sensitive hydrogels for potential drug delivery applications [17–22]. The temperature sensitive nature of PDEAAm makes it an attractive candidate for controlled drug delivery devices. However, unlike other temperature sensitive hydrogels including PNIPAAm, it has received relatively limited attention in the literature. Reports on the synthesis of PDEAAm based hydrogels using ultraviolet (UV) polymerisation have been particularly sparse [8, 23, 24]. The feasibility of synthesising PDEAAm based copolymers using photopolymerisation is thus investigated herein and the properties of the resultant hydrogels are discussed.

Experimental details

Synthesis

The hydrogels investigated in this work were prepared by free-radical polymerisation using ultraviolet (UV) light. The monomers used were *N*,*N*-diethylacrylamide (DEAAm, Polysciences Inc.), 1-vinyl-2-pyrrolidinone (NVP, Lancaster Synthesis) and *N*,*N*-dimethylacrylamide (DMAAm, Sigma Aldrich). Poly(ethylene glycol) dimethacrylate with a molecular weight of 600 (PEG600DMA, Sigma Aldrich) was the crosslinker used and this was added at 0.1, 0.25 and 0.5 wt% of the total monomer content. To initiate the reactions, two UV light sensitive initiators were studied, namely 1-hydroxycyclohexylphenylketone (Irgacure® 184) and 2-hydroxy-1-[4-(hydroxy-ethoxy)phenyl]-2-methyl-1-propanone (Irgacure® 2959, both Ciba Speciality Chemicals). The photoinitiators were added individually at 3 wt% of the total monomer content and stirred continuously until completely dissolved. The solutions were next pipetted into silicone mouldings (W.P. Notcutt, Middlesex) which were positioned horizontally to the gravity direction under two UVA 340 UV lamps (Q-panel products). Finally the samples were cured in an enclosed environment at ambient temperature for a period of 24 h, the samples being carefully turned over after approximately 12 h to ensure that the entire surface area received the same intensity of radiation during the photopolymerisation process. Once cured, the samples were dried in a vacuum oven at 30 °C, 500 mmHg for 24 h prior to further use. Table 1 lists the hydrogel name and composition of the xerogels produced. The preparation of the linear copolymers is similar to that of the crosslinked copolymers as described above, but in the absence of crosslinker. Please note that the character 'X'-preceding the sample name will be used to denote all chemically crosslinked samples.

Attenuated total reflectance Fourier transform infrared spectroscopy

Attenuated total reflectance Fourier transform infrared spectroscopy was carried out on a Perkin Elmer Spectrum One fitted with a universal ATR sampling accessory. All data was recorded at room temperature, in the spectral range of 4000–650 cm^{-1}, utilising a 16 scan per sample cycle and a fixed universal compression force.

Thermal analysis of xerogels

Differential scanning calorimetric measurements were carried out using a TA Instruments DSC 2920 Modulated DSC (AGB Scientific Ltd). Xerogels (dehydrated form of gel) of between 8 and 10 mg were weighed out using a Sartorius scales capable of being read to five decimal places. All measurements were conducted in sealed non-hermetic aluminium pans by heating the samples at a rate of 10 °C/min from 20 to 200 °C, with an empty crimped aluminium pan being used as the reference cell. Prior to

Table 1 Name and composition of hydrogels synthesised using photopolymerisation

Hydrogel name	DEAAm (wt%)	NVP (wt%)	DMAAm (wt%)
B1	100	–	–
B2	–	100	–
B3	–	–	100
B5	90	10	–
B6	80	20	–
B7	70	30	–
B8	90	–	10
B9	80	–	20
B10	70	–	30

this, samples were heated from 20 to 200 °C at 10 °C/min to remove residual moisture and erase the effect of previous thermal history. The glass transition temperature (T_g) was considered at the mid-point temperature of the endothermic drift in the heating curves. All DSC tests were carried out under a 20 mL/min flow of nitrogen to prevent oxidation. High purity indium was used to calibrate the temperature value.

Phase transition determination

Homogeneous solutions of the physically crosslinked gels were prepared, by dissolving the xerogels at concentrations of between 1 and 5 wt% in distilled water, while applying gentle stirring with the use of magnetic stirrers to aid dissolution.

Cloud point measurements

The cloud point analysis was carried out in triplicate in a thermostable bath by immersing the solutions in 75 mm sealed glass test tubes. To ensure the absence of leakage, the test tubes were weighed before and after cloud point measurement. The temperature was gradually increased at a rate of less than 1 °C/min, after the temperature reached a few degrees below the pre-estimated cloud point temperature. Cloud points were determined visually at the point at which the solutions became totally opaque.

Modulated differential scanning calorimetry

DSC analyses were again performed using a DSC 2920 Modulated DSC (TA Instruments) containing a refrigerator cooling system. Samples of between 8 and 10 mg were transferred by syringe and 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 10 to 60 °C for each of the aqueous solutions. The DSC measurements were carried out in duplicate at a scanning rate of 1 °C/min under nitrogen atmosphere.

Swelling behaviour

The chemically crosslinked samples were first allowed to reach equilibrium swelling in distilled water at ambient temperature (20 °C). Xerogel samples with a mass of 1.3 ± 0.15 g were placed in a Petri dish; the Petri dish was filled with distilled water and placed at room temperature for 168 h. Petri dish lids and Petri seal (Diversified Biotech Ltd.) were placed on the Petri dishes to prevent evaporation. Periodically, excess polymer solution was removed after predetermined time intervals by pouring the solution through a Buchner funnel. The hydrogels were blotted free of surface water with filter paper, and the wet weight of the samples was measured using a Sartorius scale at room temperature. The samples were then re-submerged in fresh distilled water. The percentage that the hydrogels swelled was calculated using the formula below;

$$\text{Swelling}\,(\%) = W_t/W_o \times 100$$

where W_t is the weight of the swollen gel at a predetermined time and W_o is the dry mass of the gel. After swelling for 168 h, the hydrogels were transferred into Petri dishes containing distilled water at a temperature of 60 °C. At predetermined time intervals, the samples were removed and the weights calculated as described previously. The above process was continued for a number of times so as to achieve a cycle of swelling and shrinking/deswelling data. All of the swelling investigations were carried out in duplicate with pictures of the swollen samples taken after removal of the distilled water solution.

Rheological measurements

Oscillatory parallel plate rheological measurements were carried out on hydrated hydrogels using an Advanced Rheometer AR1000 (TA instruments) fitted with a Peltier temperature controller. Equilibrium swollen hydrogel samples were tested in triplicate (using individual samples) at a temperature of 20 °C using a 6 cm parallel steel plate. A strain sweep was applied from $1.8E^{-4}$ to $1E^{-3}$ at a frequency of 1 Hz, while a constant normal force of 5 ± 0.5 N was exerted on the samples. A low frequency and low strain range was adopted while all samples were blotted free of water using filter paper prior to testing in an attempt to minimise slippage.

Results and discussion

Synthesis

Photopolymerisation reactions are becoming more and more useful for medically related applications and in tissue engineering [13]. However, it is difficult and expensive to undertake photopolymerisation in an environment free of molecular oxygen, a well-known inhibitor of free-radical polymerisation [25]. This is of particular importance with regard to potential scale-up of activities thus careful consideration of photoinitiator is crucial. Irgacure 184 and Irgacure 2959 are classified as Type I initiators, and were chosen, as these types of photoinitiator usually have very short triplet lifetimes, therefore, they do not suffer extensively from oxygen inhibition [26]. *N*,*N*-Diethylacrylamide

(DEAAm) is in liquid state at room temperature and many initiators can be dissolved in it, thus facilitating bulk polymerisation. This is advantageous when compared with PNIPAAm homopolymer, which cannot be synthesised using bulk polymerisation, as NIPAAm is a solid monomer.

The DEAAm, DMAAm and NVP based homopolymers synthesised were allowed 24 h to cure. The DEAAm and DMAAm samples prepared using Irgacure 184 cured with a slightly greater consistency than the polymers based on Irgacure 2959. PVP xerogels fabricated using both initiators cured very well, with polymer scientists often including NVP in photopolymer formulations as it has been shown to dramatically reduce oxygen inhibition [13]. Following initial cloud point and MDSC analysis it was found that the PDEAAm homopolymers synthesised had LCSTs of approximately 30 °C ("Lower critical solution temperature determination" section). It is common practice to incorporate hydrophilic constituents as a means of increasing the LCST of negative temperature sensitive systems, with DMAAm and NVP being the materials of choice in this study. The DEAAm/NVP copolymers (B5–B7) synthesised using both photoinitiators resulted in transparent glass-like xerogels following 24 h exposure to the UV light source. The DEAAm/DMAAm copolymers (B8–B10) prepared using Irgacure 184 were similar in appearance to the DEAAm/NVP samples; though the samples fabricated using 2959 were again not quite as uniform or smooth, therefore, use of an inert environment may be necessary when synthesising such samples with the latter photoinitiator. Alternatively, higher light intensities could be employed as this has been shown to increase efficiency when carrying out UV polymerisation in non-inert environments [27].

Attenuated total reflectance Fourier transform infrared spectroscopy

PDEAAm contains hydrophilic amide groups as well as hydrophobic vinyl backbones and diethyl side groups in the main chain structure, as depicted in Fig. 1.

ATR–FTIR was used to confirm the structure of the DEAAm, DMAAm and NVP monomers, as well as the resulting homopolymers and copolymers. Each of the monomers exhibited two very strong bands in the region of 1700–1600 cm^{-1}. More specifically, DEAAm monomer exhibited a C=O stretching band at 1648 cm^{-1} and C=C stretching band at 1607 cm^{-1} as shown in Fig. 2. As expected, the C=O and C=C peaks for DMAAm were similarly positioned, at 1647 and 1610 cm^{-1}, respectively. NVP monomer had peaks at 1694 (C=O) and 1625 cm^{-1} (C=C), all of which is in good agreement with the literature [28–30]. The disappearance of the C=C bond stretching

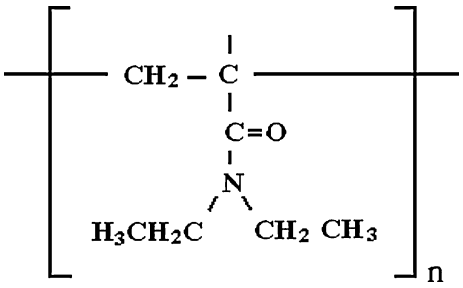

Fig. 1 Chemical structure of PDEAAm

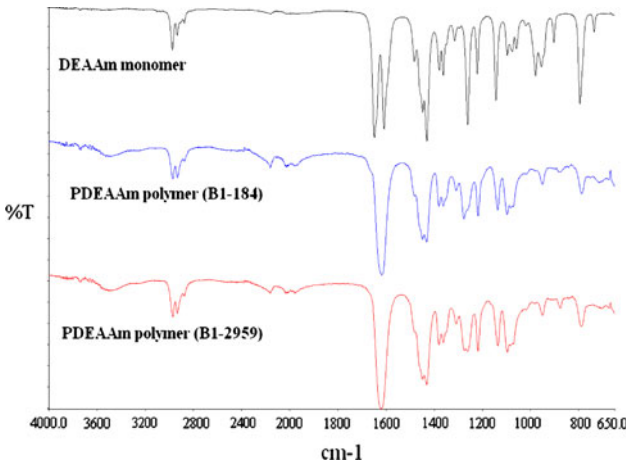

Fig. 2 Overlaid FTIR spectra for DEAAm monomer and PDEAAm homopolymer (B1) synthesised using both Irgacure 184 and Irgacure 2959

vibration in each of the homopolymer spectrum indicates that the monomers have been polymerised. PDEAAm displays an intense peak at 1650–1640 cm^{-1} due to stretching of the secondary amide, according to Hiratani and Alvarez-Lorenzo [8]. In the case of PVP, a broad C=O stretching band can be found at 1675 cm^{-1} [29], while DMAAm has been reported to exhibit C=O stretching at 1618 cm^{-1} [31]. Broad C=O peaks found at 1618, 1611 and 1646 cm^{-1} for PDEAAm, PDMAAm and PVP homopolymer, respectively, further indicate successful polymerisation. The initiator used was found to have a negligible effect on the peak positions and intensities for each of the samples. Ma et al. [32] states that PDEAAm exhibits a broad C=O band at 1636 cm^{-1} and two characteristic bands of C–H vibration with almost the same intensity at about 1457 cm^{-1} and 1646 cm^{-1} which belong to the bands of $–CH_2–$ and $–CH_3$ groups. In each of the copolymer spectra, broad C=O bands (1618 cm^{-1}) were found but the C=C stretching bands at 1607 cm^{-1} typical of the monomers were not evident. Furthermore the PDEAAm/PVP and PDEAAm/PDMAAm copolymers exhibited bands at approximately 1432 and 1380 cm^{-1} corresponding to the typical peaks of PDEAAm. Given that

DEAAm was the main constituent of all of the copolymers synthesised; this signifies that successful polymerisation of the samples had taken place.

Thermal analysis of xerogels

The homopolymers synthesised in this study had glass transition temperatures (T_gs) of 122, 81 and 69 °C, respectively, for the PVP, PDMAAm and PDEAAm (see Fig. 3). These polymers exhibited distinctive endotherms indicating that they are amorphous, as semi-crystalline materials do not usually exhibit such clear glass transition temperatures. Generally, amorphous polymers are stiff, brittle and clear in the virgin state and this is typical of the xerogels synthesised. Single individual endotherms were observed for the T_gs of the PDEAAm/PVP and PDEAAm/PDMAAm samples, thus the materials can be characterised as random copolymers. The T_gs of the copolymers were all in a similar range as that of PDEAAm homopolymer (58–62 °C for the NVP based copolymers and 64–67 °C for the DMAAm based copolymers), as would be expected given that the negative temperature sensitive material was the major component in the copolymers. No exothermic melting curve or thermal degradation was observed for each of the xerogels in the range of temperatures tested. This is also typical of amorphous polymers, as they do not possess a sharp melting point but instead soften gradually as the temperature rises.

Lower critical solution temperature determination

Numerous methods have been used to examine the transition temperature of thermosensitive polymers, with differential scanning calorimetry and cloud point measurement traditionally being among the most popular techniques. Generally the cloud point temperature is taken at the onset of turbidity; however, in this study not all samples were completely clear at room temperature, thus the measurement was taken at the point at which the solutions became totally opaque. It was found that the xerogels dissolved after 2 weeks under gentle stirring at the two lowest polymer concentrations (1–2 wt%). However, upon close inspection, it was apparent that the polymers had not fully dissolved at higher concentrations (3–5 wt%) after this time period. Control of the tacticity is very important with physically crosslinked PDEAAm based materials, as it is known to have strong influence on the solubility of the polymer [33]. Linear PNIPAAm has a LCST of approximately 32 °C in pure water, while the transition temperature of PDEAAm is also often reported in close proximity to this temperature [5–9]. In this study, the cloud point for PDEAAm homopolymer was recorded at approximately 28 °C. Adjustment of LCST to near body temperature is essential particularly for smart drug delivery applications. The LCST of the thermosensitive gels was thus controlled by adjusting the relative hydrophobicity, which was achieved by copolymerising DEAAm monomer with NVP and DMAAm monomers at varying feed ratios. This resulted in an increase in the LCST of the synthesised copolymers, which became more pronounced on increasing NVP/DMAAm content as illustrated in Table 2. All DSC measurements were carried out in duplicate on individual samples and the average values recorded (please note that LCST values of these individual runs did not differ by more than 0.5 °C in any instance).

The rate at which PDEAAm solutions are heated has been previously shown to have significant effect on the optical LCST measurement, while the transition temperature is also dependent on polymer concentration, using such techniques. However, large variations in polymer concentration (0.5–20 wt%) do not significantly affect transition temperature measurements (peak maximum values) using differential scanning calorimetry, as particle size does not influence LCST values measured using this method [34]. Therefore, MDSC analysis was used to further quantify the findings of the cloud point testing. Figure 4 shows a representative scan of 2 wt% aqueous poly(*N*,*N*-diethylacrylamide) solution, which displays a LCST peak maximum value of approximately 29 °C. The PDEAAm/PVP and PDEAAm/DMAAm copolymers were again found to exhibit increased LCST values at higher NVP/DMAAm feed ratios, with the MDSC values in good agreement with cloud point analysis results (Table 2). Importantly, a number of samples exhibited LCSTs in the region of 37 °C, which is advantageous for potential controlled drug delivery applications. As presented in Table 2, the initiator used had little effect on the LCST onset or peak values recorded using MDSC, with values differing by less than 1 °C in all cases.

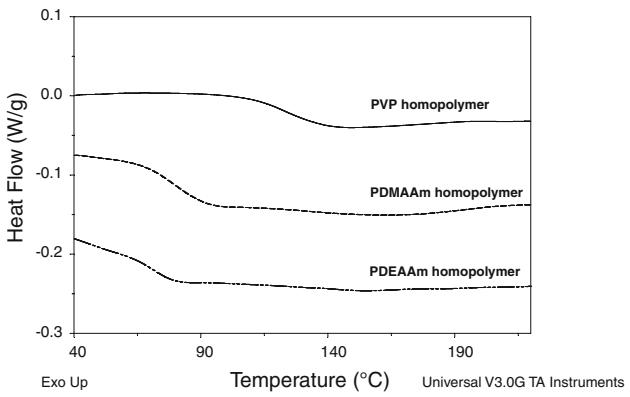

Fig. 3 MDSC thermograms of PVP, PDMAAm and PDEAAm homopolymers synthesised using Irgacure 184

Table 2 LCSTs of DEAAm based hydrogels using cloud point and MDSC analysis

Hydrogel name	Cloud point analysis	MDSC	
	LCST (°C)	LCST onset (°C)	LCST peak (°C)
B1 (184)	28.0	28	29.0
B1 (2959)	28.0	28	28.3
B5 (184)	33.0	30.6	33.7
B5 (2959)	33.0	30.4	33.5
B6 (184)	37.0	35.0	37.0
B6 (2959)	37.0	35.5	37.5
B7 (184)	42.0	41.0	42.7
B7 (2959)	42.0	40.3	41.5
B8 (184)	33.0	30.5	33.3
B8 (2959)	33.0	31.2	33.3
B9 (184)	38.0	36.4	38.3
B9 (2959)	38.0	35.5	37.8
B10 (184)	43.0	41.5	44.1
B10 (2959)	43.0	42.3	44.3

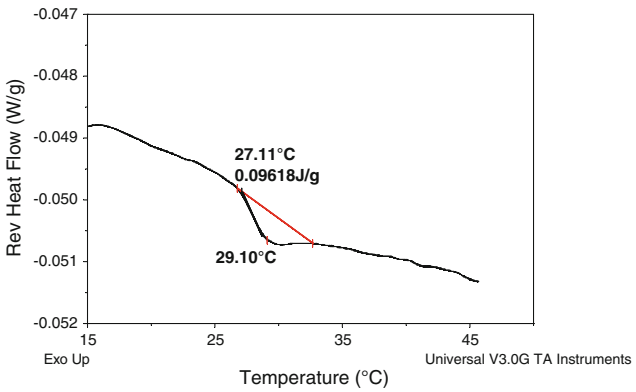

Fig. 4 LCST endotherm for 2 wt% aqueous poly(*N*,*N*-diethylacrylamide) solution

Swelling behaviour

Zhang and Zhuo [35] 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 suddenly altered stimulation, such as temperature change, is more important. The volume-changing behaviour of the negative temperature sensitive hydrogels synthesised, in response to stepwise environmental temperature change, was thus investigated to ascertain their potential for drug delivery applications. There have been a number of studies on the effect of photoinitiators on the cytocompatibility of hydrogel systems [13, 16], however, the effect of photoinitiator chosen on properties such as the degree of swelling are oftentimes overlooked. As such, the swelling behaviour of X-B7 and X-B10 gels crosslinked using 0.1 wt% crosslinking agent (with Irgacure 184 and Irgacure 2959) were initially investigated. The test temperatures were chosen based on the LCSTs of the hydrogels as determined using cloud point and MDSC analysis. Firstly the hydrogels were allowed to swell in distilled water at 20 °C (which is a number of degree Celsius below the LCST of the hydrogels) for 168 h, after which time the samples had reached equilibrium swelling. The samples synthesised using NVP and DMAAm had swelling ratios of approximately 20 and 25, respectively, and thus can be characterised as superabsorbent. Following the original swelling step, the specimens were placed in distilled water at 60 °C (which is a number of degree Celsius above the LCST of the hydrogels) and were found to undergo relatively rapid deswelling, dispelling approximately 90% of the imbibed water within 2 h. Two subsequent swelling and deswelling cycles were carried out with almost identical behaviour exhibited in both cases. As illustrated in Fig. 5, the type of initiator used had a negligible effect on the pulsatile swelling behaviour of the DEAAm/NVP samples, and this was also the case for the DEAAm/DMAAm based hydrogels. Figure 6 further demonstrates the on–off swelling capabilities of the hydrogels upon changes in the external environmental temperature.

At the deswelling temperature used, a dense white skin layer was formed on the surface of the hydrogels. This phenomenon occurs with many negative temperature sensitive hydrogels above their LCSTs. However, the formation of such a skin is generally less important in dictating release kinetics, than the relationship between the size of the mesh and incorporated drug. For example, the pattern of streptokinase release from a number of PNIPAAm/PMAA poly(methacrylic acid) copolymers was directly

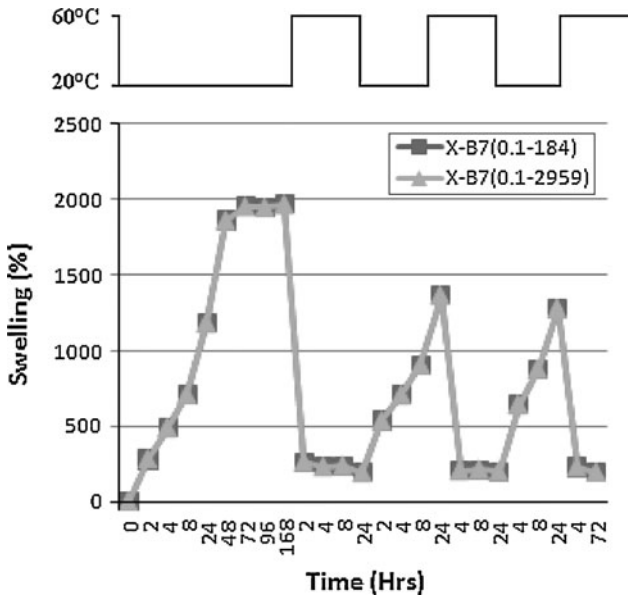

Fig. 5 Pulsatile swelling behaviour of DEAAm/NVP based hydrogels synthesised using both Irgacure 184 and Irgacure 2959, in response to stepwise temperature changes between 20 and 60 °C

related to the swelling state of the gel, irrespective of whether skin formation occurred [36]. Therefore, the effect of crosslinking degree on the swelling behaviour of the hydrogels was investigated, to allow potential tailoring of on–off release that could be adapted to active agents of differing molecular weights. Panayiotou and Freitag [10] among others have carried out work on the effect of crosslinking degree on the swelling behaviour of negative temperature sensitive hydrogels. The general rule is that a lower degree of crosslinking leads to a higher swelling ratio. Thus based on a previous study by our research group [19], the crosslinking agent was originally incorporated at 0.1 wt% of the total monomer content, to create hydrogels with high degrees of swelling, with two higher concentrations of crosslinker (0.25 and 0.5 wt%) subsequently examined. Changing the degree of crosslinking can also have a significant effect on hydrogel strength, as is discussed in "Rheological analysis" section.

The effect of altering the degree of crosslinker is most apparent in the original swelling cycle when the hydrogels were allowed to reach equilibrium swelling, as illustrated for the DEAAm/NVP samples in Fig. 7. The swelling ratios were significantly reduced for both sets of copolymer hydrogels upon incorporation of the higher concentrations of crosslinking agent. This was most apparent for the DEAAm/DMAAm gels, with the swelling ratio reducing from approximately 25 to about 7, as the PEGDMA concentration was increased from 0.1 to 0.5 wt%. In the second and third swelling cycles the hydrogels were not allowed to reach equilibrium swelling, as the swelling was carried out only for 24 h. Despite this, the crosslinker concentration again had a notable affect on the degree of swelling with this behaviour again most obvious with the DEAAm/DMAAm based samples. The pulsatile swelling behaviour was almost identical in the second and third swelling/deswelling cycles for both sets of copolymers at

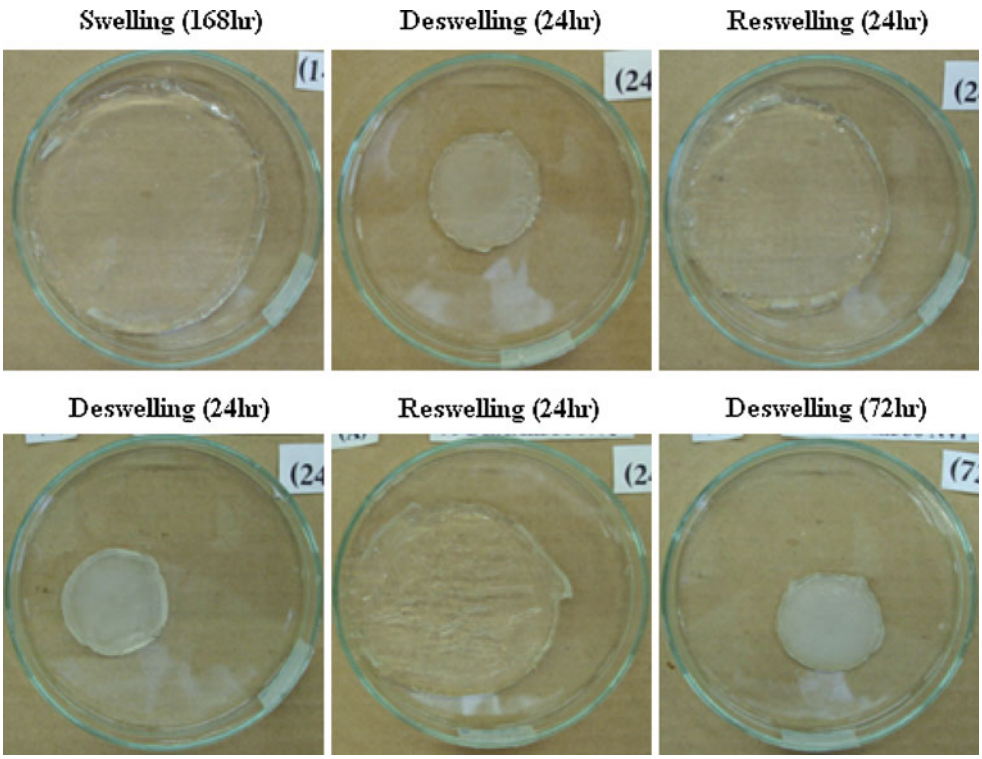

Fig. 6 Pulsatile swelling behaviour of DEAAm/NVP (X-B7) based hydrogels synthesised using Irgacure 184, in response to stepwise temperature changes between 20 and 60 °C

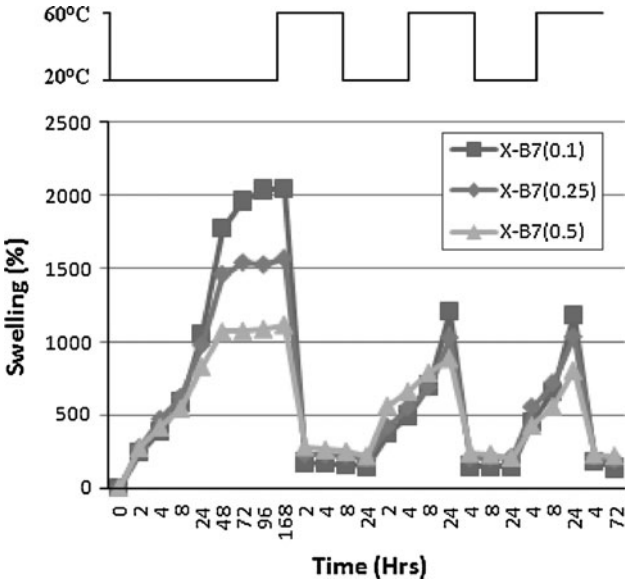

Fig. 7 Pulsatile swelling behaviour of DEAAm/NVP based hydrogels synthesised using Irgacure 184 at a variety of crosslinker concentrations, in response to stepwise temperature changes between 20 and 60 °C

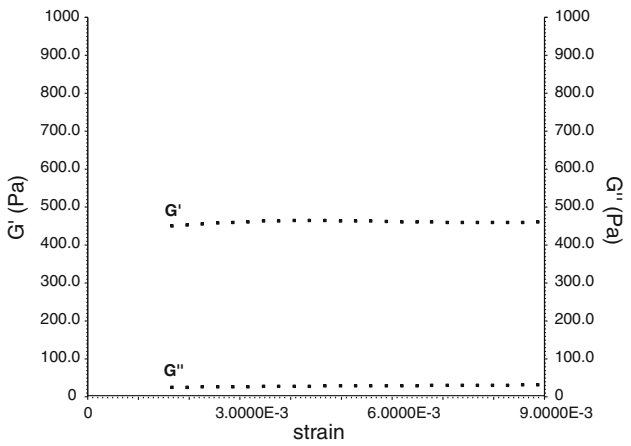

Fig. 8 Oscillatory rheological behaviour of hydrogel B7 synthesised using Irgacure 2959

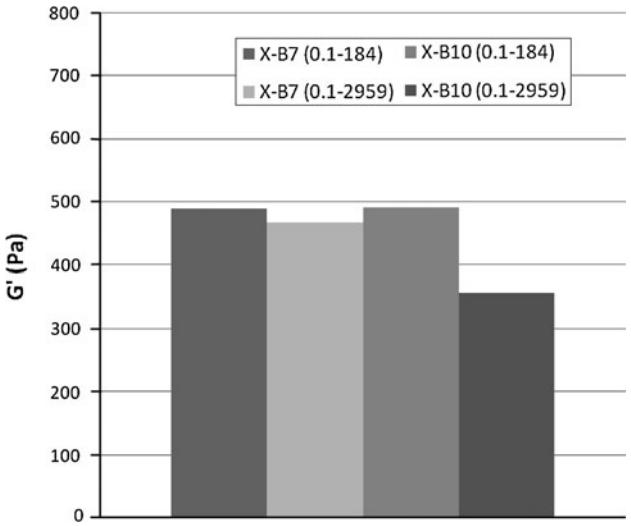

Fig. 9 Storage modulus of DEAAm/NVP and DEAAm/DMAAm based hydrogels synthesised using both Irgacure 184 and Irgacure 2959 ($n = 3$)

each concentration of crosslinking agent. This level of reproducibility is encouraging for potential on–off drug delivery applications.

Rheological analysis

The mechanical properties of hydrogels are of great importance particularly if they are to be used in controlled drug delivery applications. Rheological measurements were carried out in triplicate using individual samples and the average values tabulated. As expected storage modulus (G') values were much greater than loss modulus (G'') values for each of the samples analysed as illustrated in Fig. 8 for hydrogel B7 synthesised using Irgacure 2959. This is because the elastic response dominates, which is typical for gels and solid like materials. As negligible variation in G'' values was observed throughout testing, the mechanical behaviour was studied using G' only. Analysis was first carried out to ascertain if the type of photoinitiator chosen had an effect on hydrogel strength. The average values recorded for the DEAAm/NVP and DEAAm/DMAAm samples synthesised using both Irgacure 184 and Irgacure 2959 are shown in Fig. 9. The photoinitiator used was found to have little effect on the strength of the DEAAm/NVP hydrogels. There was a more notable difference in strength for the DEAAm/DMAAm hydrogels. As previously discussed, the Irgacure 2959 samples were not quite as uniform or smooth as the Irgacure 184 samples after the curing process. Based on these findings, use of a nitrogen blanket or light source with a higher intensity would be advisable when synthesising DEAAm/DMAAm based samples with Irgacure 2959.

Analysis was also carried out to establish if altering the ratio of crosslinker could be used as a means of improving the mechanical properties of the hydrogels. Three concentrations of crosslinking agent were studied, 0.1, 0.25 and 0.5 wt%, for DEAAm/NVP and DEAAm/DMAAm samples synthesised using Irgacure 184. As illustrated in Fig. 10, increasing the degree of crosslinker resulted in a marked enhancement in storage modulus values. The X-B7 samples yielded G' values of approximately 490, 1880 and 2400 Pa, as the crosslinking ratio was increased. The X-B10 materials exhibited a similar trend displaying G' values of approximately 490, 1280 and 2200 Pa. Chemically crosslinked hydrogels have well-defined point crosslink structures, and a higher degree of crosslinking is

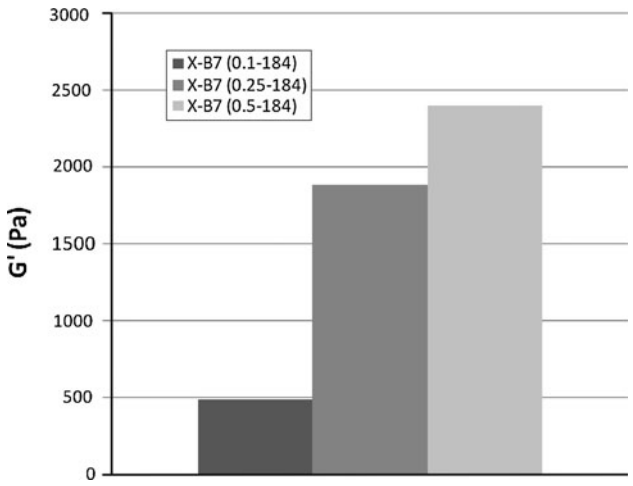

Fig. 10 Storage modulus of DEAAm/NVP based at a variety of initiator concentrations ($n = 3$)

achieved by increasing the ratio of PEG600DMA in the systems. This results in a more tightly knit structure which is responsible for the increase in strength of the samples. This almost fivefold increase in storage modulus shows the ability of manipulating the mechanical strength of these temperature sensitive hydrogels.

Conclusion

The bulk polymerisation of PDEAAm homopolymer and PDEAAm based copolymers was carried out using photopolymerisation. The use of the Type I initiators, Irgacure 184 and Irgacure 2959, allowed the synthesis to be undertaken in an air atmosphere, thus eliminating need for a nitrogen blanket. This is of particular importance with regard to potential scale-up of activities. The disappearance of the characteristic monomeric C=C bond stretching vibration using FTIR confirmed that successful polymerisation had taken place. The xerogels were stiff brittle and clear after the UV photopolymerisation process. All of the copolymers exhibited single distinctive endotherms representing the glass transition temperature, and thus can be characterised as random copolymers. By alternating the feed ratio, using PDEAAm and the more hydrophilic PDEAAm and PVP, a number of the copolymers were designed to have LCSTs of around 37 °C. We have demonstrated that the hydrogels undergo reproducible pulsatile swelling in response to environmental temperature change. Also by increasing the ratio of crosslinking agent, the mechanical properties of the novel temperature sensitive hydrogels was greatly improved.

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