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Lower critical solution temperature control and swelling behaviour of physically crosslinked thermosensitive copolymers based on *N*-isopropylacrylamide

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Abstract

In this contribution we have developed thermosensitive polymer matrices based on *N*-isopropylacrylamide (NIPAAm). Preparation of the hydrogels involved photopolymerisation of a combination of NIPAAm, 1-vinyl-2-pyrrolidinone (NVP) and distilled water, in appropriate amounts and contained a UV-light sensitive initiator called 1-hydroxycyclohexylphenylketone. As NIPAAm monomer could be readily dissolved in mixtures of liquid NVP and distilled water, the use of organic solvents was not required in the polymerisation process. Furthermore, chemical crosslinking agents are not needed in the synthesis. By alternating the feed ratio, hydrogels were synthesised to have lower critical solution temperatures (LCST) in the vicinity of 37 °C. This ability to shift the phase transition temperature of the gels provides excellent flexibility in tailoring transitions for specific uses. The transition temperature of the pseudo gels was established using cloud point measurement and modulated differential scanning calorimetry (MDSC). The chemical structure of the xerogels was characterised by means of Fourier transform infrared spectroscopy (Ftir), while swelling experiments in distilled water indicate that the swelling and dissolution behaviour of the gels is strongly temperature dependent.

Keywords: Hydrogels; Poly(*N*-isopropylacrylamide); Lower critical solution temperature; Thermosensitive polymer; Biodegradable; Controlled drug delivery

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1. 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 et al. [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].

Chemical crosslinking is a highly versatile method of creating hydrogels with good mechanical stability, which may be used in drug delivery applications [9]. However, chemically crosslinked hydrogels are non-biodegradable and the chemical crosslinking agents used in the synthesis of the gels are not known to be biocompatible, i.e., they may be toxic, carcinogenic or teratogenic [10,11]. As a result, biodegradable systems such as pseudo gels (physically crosslinked hydrogels) have garnered much of the recent attention and development in drug delivery systems because non-biodegradable systems need retrieval or further manipulation after introduction into the body [4].

Poly(*N*-isopropylacrylamide) (PNIPAAm) is the most popular of the temperature sensitive hydrogels. It has been reported that aqueous PNIPAAm water solutions and hydrogels exhibit a lower critical solution temperature (LCST) at 32 °C [6,12,13,10,14–16]. Below phase transition temperature, PNIPAAm is extremely soluble in water, however as the temperature is increased above its LCST, it becomes hydrophobic and precipitates out from the aqueous solution [17]. In this work we investigated the reversed temperature-dependent solubility of PNIPAAm based hydrogels in aqueous media. The concept consists of controlling the dissolution time of UV cured pseudo gels at physiological temperature. The rate at which these hydrogels dissolute is dependent on the LCST and this can be manipulated by alternating the hydrophobic and hydrophilic components.

2. Experimental

2.1. Synthesis of polymers

The hydrogels investigated in this work were prepared by free-radical polymerisation using ultra violet light. The monomers used were 1-vinyl-2-pyrrolidinone (NVP, Lancaster synthesis) and *N*-isopropylacrylamide (NIPAAm, TCL Europe). Both monomers 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. These solutions were then pipetted into a silicone mould (W.P. Notcutt, Middlesex) that contained disk impressions for use in swelling studies and rectangular impressions for use in Fourier transform infrared spectroscopy (Ftir). The mould was then 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 gels were carefully turned over after 3 h curing to ensure that the entire surface area received the same intensity of radiation during the photopolymerisation process. The samples were then dried in a vacuum oven at 40 °C, 500 mmHg for at least 24 h prior to use. Table 1 lists the hydrogel name and composition of each of the gels

Table 1
Name and composition of hydrogels containing NVP, NIPAAm and distilled water in their feed ratios. Irgacure 184 was used as a UV-light sensitive initiator at 3 wt% of the total monomer weight for each of these gels

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

produced. As NIPAAm monomer is a solid, PNIPAAm itself could not be synthesised by UV polymerisation using this procedure. Therefore, all tests on PNIPAAm homopolymer were carried out on Poly(*N*-isopropylacrylamide) (Polysciences Inc), which was used as received.

2.2. Preparation of aqueous solutions

Homogeneous solutions of each of the hydrogels were prepared, by weighing appropriate amounts of the xerogel and distilled water, leaving these mixtures at room temperature for a period of hours/days. Once dissolved, further amounts of distilled water were added, until solutions of appropriate concentration were achieved. These aqueous solutions were produced for subsequent use in cloud point and calorimetric measurements.

2.3. Phase transition determination

2.3.1. Modulated differential scanning calorimetry

The DSC method was among the techniques 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. 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 20 to 55 °C for each of the aqueous solutions. All DSC measurements were carried out at a scanning rate of 1 °C/min under nitrogen atmosphere. Calibration was preformed using indium as standard.

2.3.2. Cloud point measurements

Cloud point measurement was also used to investigate the transition temperature of the gels. Each solution was stirred gently before cloud point analysis to ensure that the process occurred in chemical equilibrium. The cloud point temperatures were taken 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 per minute, after the temperature reached a few degrees below the pre-estimated cloud point temperature. Cloud points were determined visually at the first sign of turbidity with an accuracy of thermometer (±0.2 °C) and the obtained results are reproducible to within 0.4 °C. All tests were carried out in triplicate and pictures were taken of the samples to show the contrasting visual appearance of the solutions above and below phase transition temperature. All pictures in this report were taken using a Fujifilm FinePix A310 digital camera with 3.1 mega pixels.

2.4. 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 seven days, using a Nicolet Avator 360 Ftir, with a 32 scan per sample cycle.

2.5. Swelling studies

The swelling characteristics of the gels were investigated in triplicate at temperatures ranging from ambient temperature to 40 °C. Samples of the cured polymer with a mass of 1.1 ± 0.35 g were placed in a petri dish; the petri dish was filled with distilled water and placed in a fan oven at the required temperature. Petri dish lids and Petri Seal (Diversified Biotech Ltd) were placed on the petri dishes while in the oven to prevent evaporation. Periodically, excess polymer solution was removed after predetermined 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 using a Sartorius scales at room temperature. The samples were re-submerged in fresh distilled water and returned to the oven. The percentage that the hydrogels swelled was calculated using the formula:

$$\text{Swelling}(\%) = W_t/W_0 \times 100$$

where W_t is the mass of the gel at a predetermined time and W_0 is the dry mass of the gel. In order to provide a clear visual demonstration of the swelling behaviour of the gels and for comparative reasons, pictures of the swollen samples were taken before the removal of the distilled water solution. This process was continued until the sample appeared to have dissolved or for up to 120 h.

3. Results and discussion

3.1. Preparation of samples

Hydrogels capable of phase transition behaviour are made of polymer chains that either possess moderately hydrophobic groups (if too hydrophobic the polymer chains would not dissolve in water at all) or contain a mixture of hydrophilic and hydrophobic segments [18]. Random copolymers of NVP/NIPAAm were photo-polymerised in the presence of small amounts of distilled water, using Irgacure® 184 as a photoinitiator. Exposure to a UV light source produces free-radicals by decomposition of the photoinitiator, which initiates polymerisation of the monomers [7]. It was found that NIPAAm monomer could be dissolved more readily in aqueous mixtures of NVP and distilled water, than in pure liquid NVP alone. This allowed greater freedom in LCST control when compared with PNIPAAm/PVP copolymers prepared in the absence of distilled water. In general, as the polymer chain contains more hydrophilic constituent, the LCST becomes higher [19,20]. 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. All samples were cured on a silicone moulding, and prior to use dried for at least 24 h in a vacuum oven. The xerogels were transparent and glass like in appearance after photopolymerisation.

3.2. Phase transition determination

The primary objective of this work was to produce hydrogels with a phase transition temperature in the region of 37 °C. As already discussed, aqueous solutions of PNIPAAm homopolymer have a phase transition temperature of about 32 °C [21], which can be determined by both DSC analysis, giving the endothermic transition peak and by cloud point measurement, giving the cloud point value [18]. The thermal analysis technique measures the heat resulting mainly from the breaking down of hydrogen bonds between water and polymer [19], while the latter method visualises the clouding of the solution due to the precipitation of the polymer, when phase separation occurs [18]. Calorimetric and cloud point measurements were carried out on aqueous PNIPAAm homopolymer in a previous work [22] and were found to be in good agreement with the literature [18–20,22–24]. As it has been extensively reported, it provides an ideal reference material for comparison with obtained results.

3.2.1. Modulated differential scanning calorimetry

The phase transition behaviour of PNIPAAm homopolymer was investigated using the reversing, non reversing and total heat flow signals of the modulated DSC. The findings show that the reversing heat flow signal yield a much more defined endotherm than the other signals and so provided much greater sensitivity in LCST determination, when compared with conventional DSC. Conventional DSC provides information about the overall heat flow measured as a function of temperature or time. Modulated DSC provides information about the reversing (heat capacity component of the total heat flow) and nonreversing (kinetic component of the total heat flow) characteristics of thermal events. This ability of Modulated DSC to divide the total heat flow into heat capacity and kinetic components permits the separation of overlapping phenomena and deconvolution of complex transitions, greater resolution without loss of sensitivity (signal-to-noise ratio at least double that of DSC) and greater ease of collection of heat capacity data when compared to conventional DSC. The sensitivity of modulated DSC in transition temperature determination is highlighted in Fig. 1. The phase transition endotherm for sample A1(L1) is undistinguishable using the total heat flow and non reversing heat flow signals. This transition is well defined using the reversing heat flow signal. Similar behaviour was observed for gels A1–A8, which were synthesised to have transition temperatures in the vicinity of physiological temperature.

In literature to date, it is important to note that authors have differed in their interpretation of the phase transition endotherm. Otake et al. [25] 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. [19] 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 number of Degrees Celsius. In this work, both peak onset and peak maximum values were recorded. Eeckman et al. suggests that copolymers of PNIPAAm should have a sharpness of phase

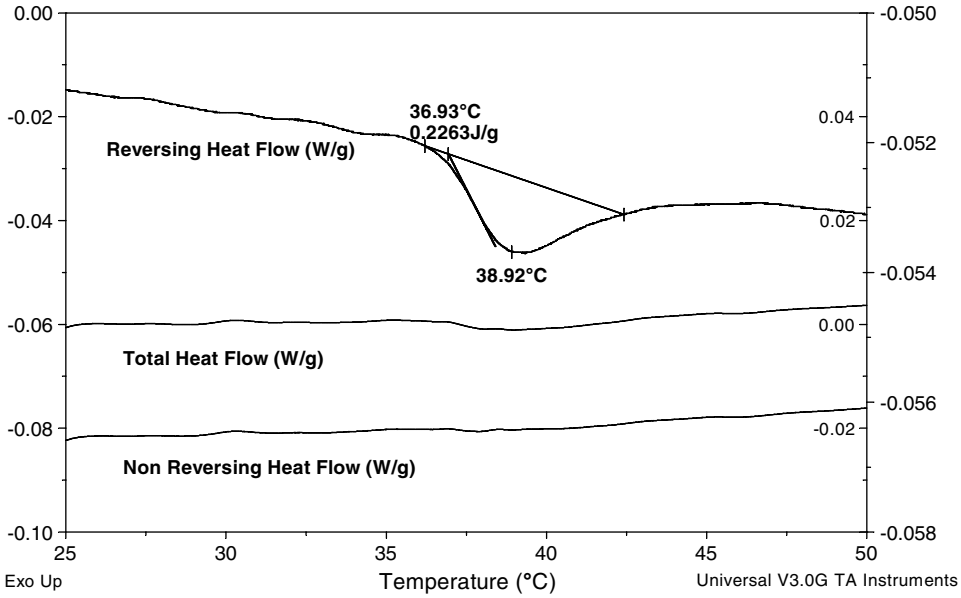

Fig. 1. Reversing heat flow, total heat flow and non reversing heat flow signals for a scan carried out on gel A1(L1) at 3 wt%.

transition comparable to that of the homopolymer with a width of DSC endotherm sufficiently small [26,27]. Gels A1(L1), A2, A3, A4(L2), A5 and A6 resemble the endotherm for aqueous PNIPAAm but are not quite as symmetrical as the homopolymer. Gels A7 and A8(L3) however, resemble a T_g curve as represented in Fig. 2. These samples are seen to have the highest percentages of NVP in the monomeric feed ratios. Eeckman et al. reported similar behaviour when observing copolymers containing PNIPAAm [27]. He noted that the increase of hydrophilic comonomer content in the copolymer is accompanied by the appearance of an asymmetry of the peaks whose tail could even extend to infinity for the higher comonomer contents. He suggests that the phenomenon could be as a result of the (unknown) polymerisation kinetics constants of the respective monomers, so polymer molecules with high hydrophilic comonomer contents are formed, those making up the right part of the transition peak.

3.2.2. Cloud point measurements

Visual observation of macroscopic phase separation upon heating was also among the employed techniques in establishing the LCST. In this investigation cloud point was determined as the temperature at which the first sign of turbidity appeared in the solution. Below cloud point temperature, aqueous copolymer solutions were clear, but upon heating the solutions became turbid because of aggregation of the polymer, over a narrow temperature range. Loh et al. [28] suggests that at a certain temperature, water becomes a poor solvent to the polymer, possibly due to the new and less polar polymer conformation, causing the prevalence of the polymer–polymer interaction and the growth of the polymer aggregates leading to phase separation.

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 [24]. The percentage NVP monomer was calculated with respect to NIPAAm monomer and an almost linear increase in phase transition temperature was seen with increasing hydrophilic component using calorimetric and cloud point techniques, as presented in Fig. 3. Cloud point and onset values from calorimetry are quite consistent, with values never differing by more than 0.5 °C. However, in some cases there is a difference of over 2 °C between calorimetric peak and onset 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 value. Samples A1(L1) and A4(L2) were selected for subsequent use in FTIR and swelling studies.

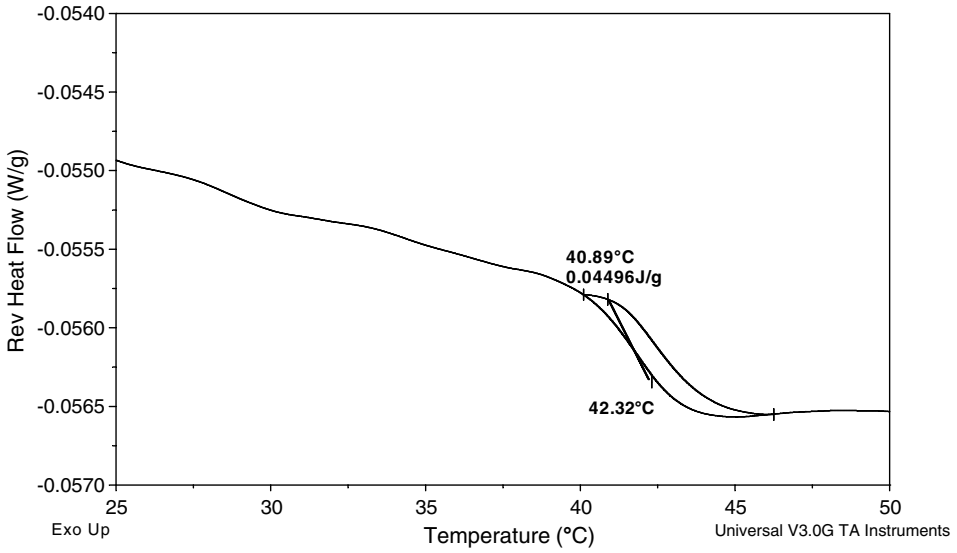

Fig. 2. Reversing heat flow signal for a scan carried out on gel A7 at 3 wt%.

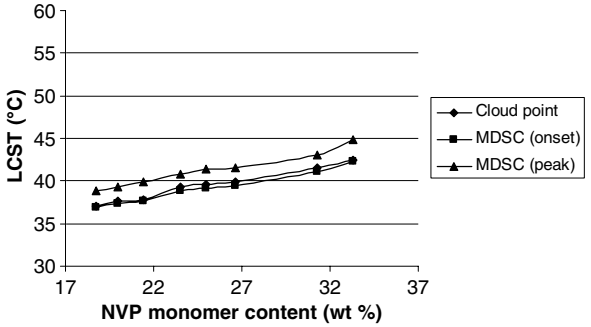

Fig. 3. LCST of 3 wt% PNIPAAm/PVP aqueous copolymer solutions with increasing NVP monomer content established by calorimetric and cloud point techniques.

3.3. Fourier transform infrared spectroscopy

PVP/PNIPAAm copolymers were characterised using Fourier transform infrared spectroscopy (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 1623 cm^{-1}, corresponding to olefinic (C=C) stretching, while the second band, due to carbonyl stretching (C=O) is located at 1700 cm^{-1}. Strong peaks in the range 800–1000 cm^{-1} corresponding to the stretching mode of vinyl double bonds were also recorded. Similar findings have been reported by Száraz et al. [29] and Sun et al. [30]. Characteristic peaks of NIPAAm monomer were noted at 1618 cm^{-1} (C=C), at 1407 cm^{-1} (CH_2=) and between 986 and 913 cm^{-1} for the vinyl group peaks. This is in agreement with work carried out by Ju et al. [12] and Kim et al [16]. 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 1641–1639 cm^{-1} for C=O, at 1538–1540 cm^{-1} for NH, and at 1386^{-1} and 1366 cm^{-1} representing the isopropyl group. These values are in good agreement with work carried out by other authors [12,31,32].

3.4. Swelling studies

Swelling experiments were preformed on circular discs of photo-polymerised polymer in distilled water, at temperatures ranging from ambient temperature to 40 °C. This covers the range of phase transition temperature of the hydrogels, as determined by cloud point measurement and modulated DSC. In physically crosslinked gels, dissolution is prevented by physical interactions, which exist between the polymer chains. Narasimhan et al. 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

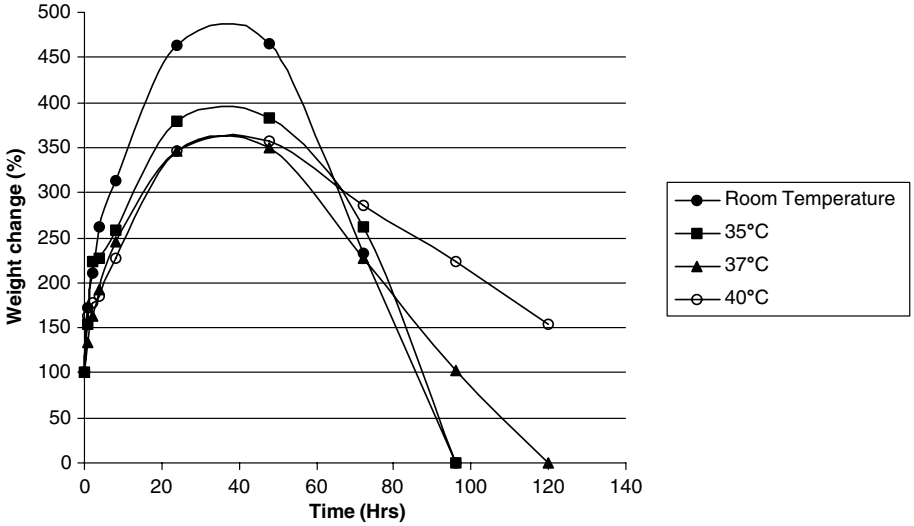

Fig. 4. Swelling behaviour of hydrogel A4(L1) at temperatures ranging from ambient temperature to 40 °C.

eventually dissolved [33]. Similar behaviour was observed for UV cured PVP pseudogels investigated in a previous work [2]. Samples prepared from 100% NVP were found to absorb an amount of water one to two times their initial mass during the swelling phase. Thereafter a dissolution phase followed in which the gel fully dissolved. All samples reached their maximum swollen weight from 0 to 4h, which would also indicate rapid dissolution. The dissolution process can be understood as the transformation undergone by the polymer from an entangled gel-like phase to a disentangled liquid solution. With increasing temperature, a reduction in dissolution time was noted. This is a common property of most physically cross-linked polymers, as they increase their water-solubility as the temperature increases. Polymers with LCST however, decrease their water-solubility as the temperature increases and are called negative temperature sensitive hydrogels.

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; significantly less water soluble; or water insoluble; depending on the composition of the gel. The use of distilled water in the synthesis did not appear to have an effect on the sharpness of the transition temperature of the gels. Hydrogel A1(L1) clearly displays inverse temperature solubility, as represented in Fig. 4. A phase transition temperature of 37 °C was established by cloud point measurement for the gel, while onset and peak values were recorded at 36.93 °C and 38.92 °C, respectively using modulated DSC. The gel reached its maximum swollen weight between 24 and 48 hrs 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. 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 value. At 40 °C, which is above the transition temperature established by both cloud point and MDSC, the samples had still not dissolved after 120 h. Similar temperature sensitive swelling behaviour was observed for gel A4 (L2). Any molecules that can form hydrogen bonds to each other can alternatively form hydrogen bonds to water molecules [34]. Because of this competition with water molecules, the hydrogen bonds formed between two molecules dissolved in water are relatively weak. It is generally believed that the phase transition behaviour of PNIPAAm based hydrogels in aqueous solutions is strongly related to the destabilisation of hydrogen bonds between water molecules and amide groups with increasing temperature, probably induced by the presence of the hydrophobic isopropyl group and backbone [35,36].

4. Conclusion

In summary, our concept consists of controlling the dissolution time of UV cured pseudo gels. It is

hoped that the solubility properties of the thermosensitive hydrogels can be used as a means of controlling release in orally delivered drug devices. Further work must be undertaken in order to investigate the effect of different pH solutions on the phase transition temperature of the copolymers, as it has been known to significantly depress the LCST. By doing so, it is hoped to design drug loaded gels which will dissolve at a predicted rate in given media, depending on temperature.

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