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Synthesis and characterization of grafted thermosensitive hydrogels for heating activated controlled release

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Abstract

Poly(*N*-isopropylacrylamide), PNIPAAm, hydrogels are negatively thermosensitive which means that they have an expanded hydrogel structure at low temperatures and a shrunken structure at high temperatures. Based on this negative thermosensitivity of PNIPAAm, a drug delivery system with PNIPAAm oligomers grafted onto poly(hydroxyethyl methacrylate) PHEMA, a thermally nonresponsive polymer was designed. Poly(hydroxyethyl methacrylate-g-*N*-isopropylacrylamide), P(HEMA-g-NIPAAm) hydrogels were synthesized to control the release of an imbedded drug. This new grafted system exhibited high diffusivity at temperatures greater than the lower critical solution temperature (LCST) of the PNIPAAm oligomers. Utilizing PNIPAAm's LCST of approximately 34 °C, the release rate was controlled by the temperature of the release medium. The LCST of PNIPAAm was tuned by making copolymers with hydrophobic butyl methacrylate (BMA). Theophylline and inulin release profiles were studied using PHEMA, PNIPAAm and P(HEMA-g-NIPAAm) at three temperatures with drug diffusion coefficients determined as a function of temperature and drug type. The molecular weights between crosslinks and mesh sizes of PHEMA hydrogels were calculated using Flory–Rehner and rubber-elasticity theories.
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Keywords: Negative thermosensitivity; *N*-isopropylacylamide; Grafted system; Positive thermal response

1. Introduction

Smart or intelligent controlled drug delivery systems have been major areas of research over the past few decades. Therapeutically, the advantages of these systems include maximizing drug effectiveness, avoiding side effects and decreasing the frequency of administration (Kost and Langer, 2001; Kikuchi and Okano, 2002; Brannon-Peppas, 1997; Brazel and Peppas, 1999). Recently much attention has been focused on controlled release systems developed from environmentally responsive polymer networks exhibiting reversible swelling behavior (Ju et al., 2001; Dong et al., 1992). Due to their unique properties, these environmentally responsive polymers, such as thermoresponsive poly(*N*-isopropylacrylamide) or PNIPAAm have been investigated as controlled drug release carriers, recyclable absorbents, enzyme immobilization networks, membranes for chemical separation and biomaterials (Bae et al., 1989; Dong and Hoffman, 1991; Okuyama et al., 1993; Piskin, 2005). It is well known that aqueous solutions of crosslinked PNIPAAm exhibit an abrupt volume change at its lower critical solution temperature (LCST) of 34 °C. It exhibits negative thermal response which means that below its LCST, PNIPAAm chains hydrate to form an expanded structure with a large mesh size enabling diffusion and above its LCST these chains dehydrate to form a shrunken structure with a small mesh size. Another important and useful feature of PNIPAAm is the ability to control its LCST by the addition of hydrophilic or hydrophobic comonommers (Feil et al., 1993). Although thermoresponsive networks have been shown to allow pulsatile or triggered release, they have found relatively few *in vivo* applications, due at least in part to the negative thermal response and the lack of biological stimuli to cause a decrease in temperature to trigger release.

Based on PNIPAAm's sharp transition and negative thermosensitivity, the purpose of this study was to synthesize short polymeric chains or oligomers based on NIPAAm, characterize them and study grafting reactions to develop a novel thermosensitive grafted hydrogel. By grafting the NIPAAm oligomers to a PHEMA hydrogel, the thermosensitivity is switched to a positive

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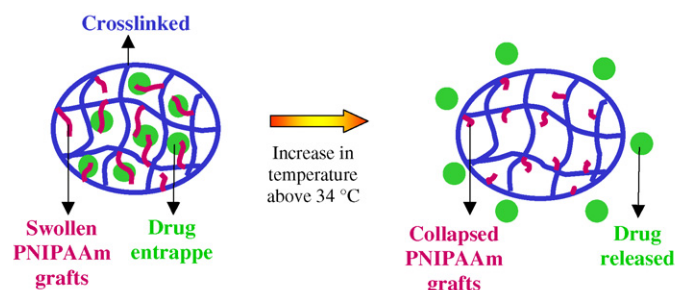

Fig. 1. Schematic of the proposed grafted system.

response, as the expanded grafts at low temperatures block diffusion, while the collapsed oligomers open mesh space for drug release as the grafted hydrogel is heated (Fig. 1). The grafted system developed here is envisioned as part of a magnetothermally triggered system (Carroll et al., 2003; Brazel et al., 2006) where external heating causes the release of medication.

2. Experimental

2.1. Materials

The monomers used were *N*-isopropylacrylamide (NIPAAm), 2-hydroxyethyl methacrylate (HEMA) (both from Acros Organics, Fair Lawn, NJ) and butyl methacrylate (BMA) (Aldrich Chemical Company Inc., Milwaukee, WI). Inhibitors were removed from HEMA and BMA by passing the liquid through a De-hibit® column (Aldrich Chemical Company Inc., Milwaukee, WI). NIPAAm, redox initiators ammonium persulfate (AmPS) and sodium metabisulfite (NaMBS) (Acros Organics, Fair Lawn, NJ), crosslinking agent methylenebisacrylamide (MBAAm), chain transfer agent 2-aminoethanethiol hydrochloride (AESH) (Acros Organics, Fair Lawn, NJ), activating agent acryloyl chloride (Aldrich Chemical Company Inc., Milwaukee, WI) and solvents tetrahydrofuran (THF) and methanol (Fisher Scientific, Fair Lawn, NJ) were all used as received.

2.2. Synthesis of oligomers and hydrogels

Oligomers of NIPAAm were synthesized by free radical polymerization of NIPAAm using a 50/50 volumetric mixture of water and methanol as the solvent. Monomer was dissolved at 5 wt.% in this solvent, nitrogen gas was purged through the mixture, and AmPS and NaMBS were each added at 5 mol% of the monomer content. After 24 h of polymerization at room temperature (25 °C), the reaction was terminated by the addition of 5 mol% AESH. Oligomer samples precipitated during the reaction were recovered by decanting the solvent and drying in a vacuum desiccator. Crosslinked PNIPAAm samples were also prepared by free radical polymerization of NIPAAm in 50% aqueous methanol using 1 mol% MBAAm as crosslinker and 1 wt.% each of AmPS and NaMBS as initiators. The mixture was poured between two siliconized glass plates separated by 8 mm thick Teflon® spacers to obtain samples of uniform thickness. The reaction was carried out at room temperature (25 °C) for 24 h. The gels were then cut into discs (25 mm in diameter and 8 mm in thickness). These discs were rinsed thoroughly in distilled water for a week to leach out excess solvent and unreacted monomers. P(NIPAAm-co-BMA) hydrogel samples using weight BMA fractions of 0.02, 0.05 and 0.1 were prepared using the same procedure. PHEMA hydrogels were also synthesized using the same procedure using pH 8 buffer in place of aqueous methanol as the solvent.

2.3. Characterizing, functionalizing and grafting oligomers

The molecular weight distribution of the synthesized NIPAAm oligomers was determined using gel permeation chromatography (system controller SCL-10A VP and Liquid controller LC-10AT VP, Shimadzu Scientific Instruments, Norcross, GA). The NIPAAm oligomers formed in the 5% solution were found to have a weight average molecular weight, $\bar{M}_w$ of around 3040 relative to polystyrene. These oligomers were then functionalized or activated by adding 5 mol% acryloyl chloride to the oligomers. The reaction was carried out while purging nitrogen gas through the mixture in an ice bath at a temperature of 4 °C for 1 h. In the subsequent step, 1 wt.% oligomers were incorporated into a network by free radical copolymerization of the acrylated oligomers with HEMA monomer using 1 mol% of crosslinking agent MBAAm and 1 wt.% each of redox initiators AmPS and NaMBS in pH 8 buffer. Assuming complete reaction, the resulting hydrogel had 1 mol of grafted NIPAAm oligomers per 100 mol of HEMA. PHEMA, PNIPAAm and P(HEMA-g-NIPAAm) hydrogel discs were dried in a desiccator under vacuum until reading a constant dry weight.

2.4. Swelling behavior

P(NIPAAm) and P(NIPAAm-co-BMA) hydrogel discs were equilibrated in deionized water at temperatures ranging between 5 and 40 °C and their respective weights (W_s) noted at each temperature. After immersion in water at a desired temperature, each polymer gel was removed from the water and blotted with Kimwipes® to remove excess water on the surface of the gel. Each gel was repeatedly weighed over a course of days and reimmersed in water at a fixed temperature until the hydrated weight reached a constant value. It was then reequilibrated at another temperature. The gels were then dried in a desiccator under vacuum until reading a constant dry weight (W_d). The equilibrium weight swelling ratios (q) were calculated as W_s/W_d and the equilibrium polymer weight fractions were found as $1/q$.

2.5. Characterizing hydrogel LCST

To further confirm the transition temperature of PNIPAAm based hydrogels, obtained by swelling data, differential scanning calorimetry (Model 2920MDSC, TA Instruments, Newcastle, DE) was performed on swollen samples to determine their LCST. PNIPAAm, P(NIPAAm-co-2 wt.% BMA) and P(HEMA-g-NIPAAm) hydrogels were equilibrated in water at 5 °C before conducting DSC experiments. The samples were cooled to 5 °C using liquid nitrogen and then heated to 45 °C at a temperature ramp of 2 °C/min.

2.6. Characterizing hydrogel microstructure

Elastic moduli were obtained for hydrated samples using an Instron® automated materials testing system (Model 5581, Instron Corp., Norwood, MA). A strain rate of 0.5 in./min was used on dogbone-shaped samples. Stress–strain data and equilibrium swelling data were used to characterize the microstructure of hydrogels and determine the molecular weight between crosslinks, $\bar{M}_c$, and the mesh size, ξ, available for diffusion of imbedded solutes or drugs through the polymer gels. Rubber-elasticity theory derived from equations of state relating the change in dimensions resulting from the swelling and deformation of a crosslinked network states that young's modulus is directly proportional to the density of crosslinks was used to calculate $\bar{M}_c$ in the PHEMA and P(HEMA-g-NIPAAm) networks from equilibrium swelling and Instron data (Flory, 1953). Using this theory, $\bar{M}_c$ can be determined from mechanical stress experiments through:

$$E\nu_{2,s}^{-1/3} = \mathrm{RT}\rho_{2,r}\left(\frac{1}{M_c} - \frac{2}{M_n}\right)\left(\frac{\nu_{2,s}}{\nu_{2,r}}\right)^{1/3} \quad (1)$$

In this equation, E is the tensile modulus of the hydrogel sample obtained by stress–strain data, R the universal gas constant, T the absolute temperature and $\rho_{2,r}$ is the density of the hydrogel in a relaxed state (freshly formed). The parameters $\nu_{2,r}$ and $\nu_{2,s}$ are the polymer fractions in the relaxed and equilibrium swollen states, and $\bar{M}_n$ is the number average linear molecular weight of the polymer chains prior to crosslinking whose value was estimated to be 100,000.

The Mesh size, ξ, is given by (Oral and Peppas, 2004):

$$\xi = (\nu_{2,s})^{-1/3}(r_o^2)^{1/2} \quad (2)$$

Here the average end-to-end distance of the polymer segments between successive crosslinks is given by

$$(r_o^2)^{1/2} = \left(\frac{2\bar{M}_c}{M_r}\right)^{1/2} C_n^{1/2} l \quad (3)$$

Here M_r is the molecular weight of a single repeating unit (130.4 for PHEMA), C_n the characteristic ratio for the polymer which was determined as 6.9 for PHEMA by Dušek and Sedláček (1969). l is the distance between two backbone carbon atoms (1.54 Å). $(r_o^2)^{1/2}$ is the average end-to-end distance of the polymer chains between two consecutive crosslinks in their unperturbed state.

2.7. Drug loading

PHEMA, PNIPAAm and P(HEMA-g-NIPAAm) hydrogel discs were loaded with theophylline by equilibrium partitioning in a 40 mL theophylline solution of concentration 2 g/L for 10 days at room temperature 25 °C. Inulin was loaded into PHEMA and P(HEMA-g-NIPAAm) gels by adding 3 wt.% inulin with respect to the monomer into the polymerization mixture while synthesizing the crosslinked network. In each case, the drug loaded hydrogels were dried to constant weight under vaccum.

2.8. Drug release experiments

In vitro drug release experiments were performed in a 6-chambered thermostatted USP type II dissolution cell system (Model 2100C, Distek, North Brunswick, NJ) connected to a six-line cassette pump and a UV spectrophotometer (Model UV-2401 PC, Shimadzu Scientific Instruments, Norcross, GA). The cells in the dissolution system were each filled with 1 L deionized water (release medium) and had paddles rotating at 100 rpm. The temperature of the dissolution tank was equilibrated at the desired temperature and the drug loaded discs were dropped into the cells to begin the experiment. The cassette pump was connected in such a way that it continuously pumped a small volume of solution from the cell into a flow-through cuvette and back into the cell. This cuvette was placed in a UV–vis spectrophotometer operated in the kinetics mode where absorbance readings were periodically measured as a function of time. Drug release experiments were conducted for about 10–12 h until the concentration stabilized. All experiments were done in triplicate to determine reproducibility of the data. Using the absorbance values obtained from the spectrophotometer and calibration plots for each drug fitted to Beer's law (theophylline 275 nm, inulin nm), the amount of drug released was determined as a function of time. Drug release experiments were conducted at 12, 25 and 37 °C for PHEMA, PNIPAAm and P(HEMA-g-NIPAAm) hydrogels loaded with theophylline or inulin.

3. Results and discussion

3.1. Swelling behaviour

Fig. 2 shows the equilibrium polymer weight fraction as a function of temperature for PNIPAAm based gels and illustrates their LCST behavior. The polymer weight fractions of PNIPAAm hydrogels which are less than 0.1 at temperatures lower than 34 °C suddenly rise up to as much as 0.6 at temperatures above 34 °C. At 34 °C which is the LCST of PNIPAAm, the curve bends sharply depicting the sharp transition of PNIPAAm. P(NIPAAm-co-BMA) hydrogels also show similar behavior with low polymer weight fractions at temperatures below their LCSTs and a transition to high polymer weight fractions at tem-

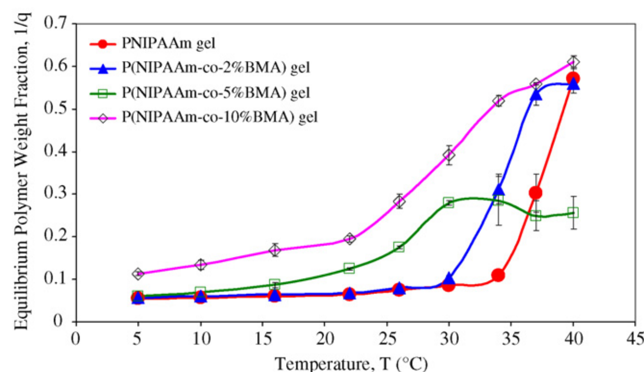

Fig. 2. Equilibrium polymer weight fractions of P(NIPAAm-co-BMA) hydrogels measured at different temperatures. Error bars indicate standard deviation for three samples. Where not shown, error bars are smaller than the data symbols.

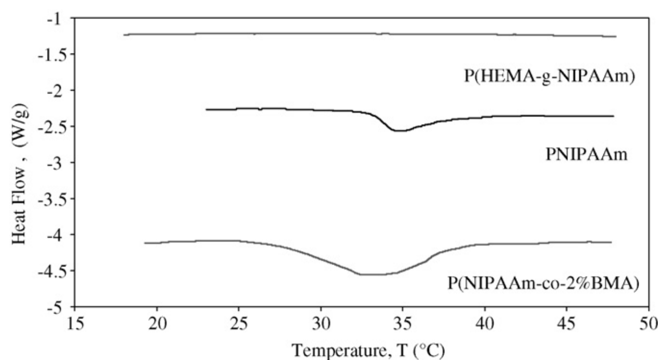

Fig. 3. DSC Thermograms of PNIPAAm, P(NIPAAm-co-2 wt.% BMA) and P(HEMA-g-NIPAAm) to investigate the LCST.

peratures above their LCSTs. Equilibrium swelling data can therefore be used to predict the approximate LCST of the polymer. It can be observed from the graph in Fig. 1 that with the increase in BMA content in the P(NIPAAm-co-BMA) hydrogels, the LCST of the polymer decreased. These results thus confirm the ability to modify the LCST of PNIPAAm by the addition of hydrophobic comonomers (Bae et al., 1989).

3.2. Differential Scanning Calorimetry

Fig. 3 shows DSC thermograms for PNIPAAm, P(NIPAAm-co-2 wt.% BMA) and P(HEMA-g-NIPAAm) hydrogels. The LCST was determined to be around 34 °C for PNIPAAm and around 33 °C for P(NIPAAm-co-2% BMA). These results were close to the approximate LCSTs obtained by equilibrium swelling experiments. P(HEMA-g-NIPAAm) samples were also run but no endothermic peaks indicative of LCSTs were observed. This could be because of the reduced content of thermoresponsive groups (NIPAAm oligomers) in each of these samples that makes an already small endotherm undetectable beyond the detection limits of standard DSC.

3.3. Hydrogel Microstructure

The mesh size of PHEMA, which was synthesized along with inulin during the crosslinking reaction, was also calculated to determine whether the presence of the model drug inulin affected the mesh size as the polymer formed around the drug. Mesh sizes of P(HEMA-g-NIPAAm) either synthesized with or without inulin were also calculated by the same procedure. The molecular weights between crosslinks, $\bar{M}_c$ and mesh size, ξ, of the PHEMA and P(HEMA-g-NIPAAm) networks with and without inulin, are listed in Table 1. There was a difference in the $\bar{M}_c$ of PHEMA with and without inulin which was compensated by a difference in the polymer fractions resulting in the same mesh size of 51 Å for PHEMA samples both with and without inulin. This confirms that the presence of inulin during the crosslinking reaction did not have a significant effect on either the polymerization reaction or the organization of chains during the reaction. The mesh sizes for both P(HEMA-g-NIPAAm) with and without inulin were determined to be 67 Å. The mesh size calculations for the grafted system did not include the grafts.

Table 1
Molecular weight between crosslinks and network mesh size of PHEMA and P(HEMA-g-NIPAAm) with and without inulin at 25 °C and equilibrated in deionized water

Hydrogel	Molecular weight between crosslinks, $\bar{M}_c$	Mesh size, ξ (Å)
PHEMA	6,000	51
PHEMA with inulin	5,000	51
P(HEMA-g-NIPAAm)	10,900	67
P(HEMA-g-NIPAAm) with inulin	11,000	67

The difference in mesh sizes for PHEMA and P(HEMA-g-NIPAAm) could be due to the presence of NIPAAm oligomers during polymerization reaction of P(HEMA-g-NIPAAm) which would cause a steric hinderance to crosslinking leading to a larger mesh size. It is important to note the sizes here, especially compared to the molecular sizes of theophylline (3.78 Å am Ende and Peppas, 1997) and inulin (15.2 Å Pappenheimer et al., 1951). The Mesh size at equilibrium controls the maximum drug diffusion coefficients during the release process.

3.4. Drug Release Behavior

The effect of polymer structure and composition on the release behavior of model drugs was observed at temperatures above and below the LCST of PNIPAAm. Drug release profiles for PNIPAAm, loaded with theophylline by equilibrium partitioning provide further proof of PNIPAAm gels' negative thermosensitivity (Fig. 4). At temperatures below the LCST of PNIPAAm (12 and 25 °C), the release is faster as the polymer chains are expanded and hence the mesh size is large. At temperatures above its LCST, the polymers contract thereby decreasing the mesh size so the rate of drug release is much slower. For release at 12 and 25 °C, the gels released most of the drug within 3 h of starting the experiment after which there was no change in concentration indicating completion of release. The slight difference in release rates between 12 and 25 °C is because of the difference in swelling ratios at these temperatures. At 37 °C, the gels were still releasing the drug even after 6 h exhibit-

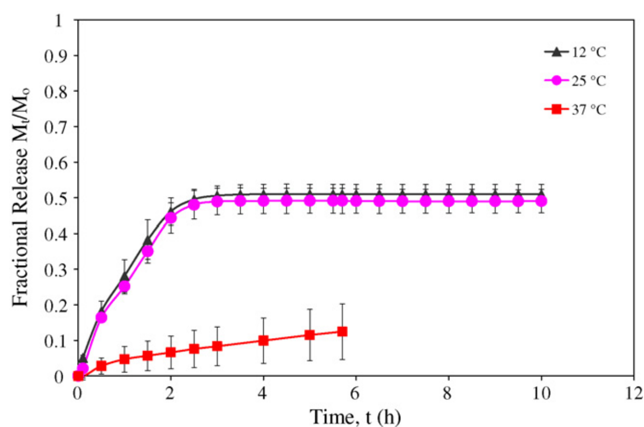

Fig. 4. Theophylline release profile for PNIPAAm hydrogels at three temperatures. DI water was used as the release medium. Error bars indicate the standard deviation for three samples.

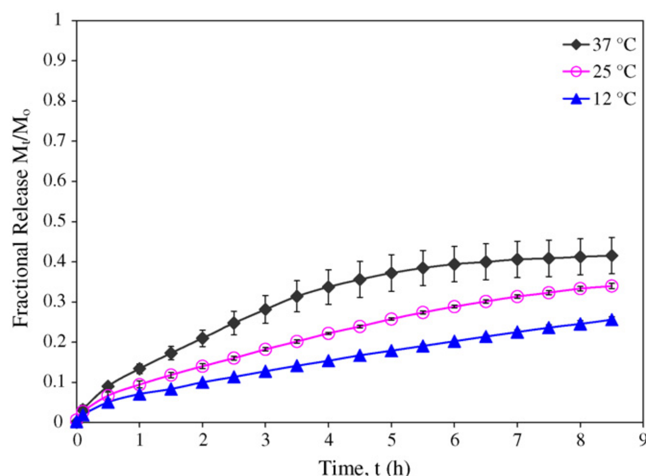

Fig. 5. Theophylline release profile for release of theophylline from PHEMA hydrogels at three temperatures. DI water was used as the release medium. Error bars indicate the standard deviation for three samples. Where not shown, error bars are smaller than the data symbols.

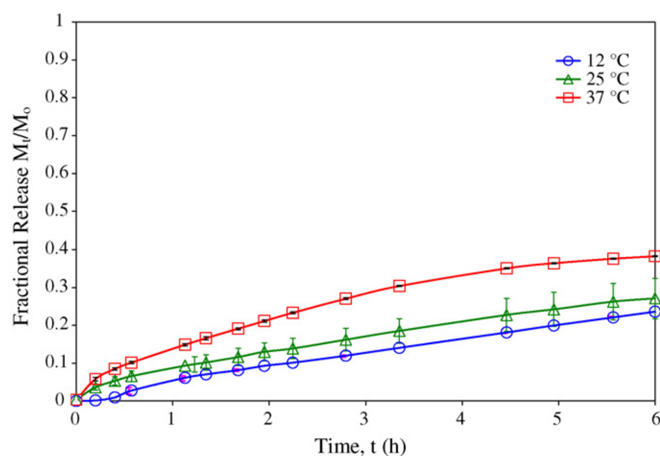

Fig. 6. Theophylline release profile for release of theophylline from P(HEMA-g-NIPAAm) hydrogels at three temperatures. Error bars indicate standard deviation for three samples. Where not shown, error bars are smaller than the data symbols.

ing a much slower rate as compared to the release rates at 12 and 25 °C. This difference in release rate was further quantified by calculating the drug diffusivity for release at these three temperatures. The drug diffusion coefficients for release of theophylline from PNIPAAm hydrogels at 12 and 25 °C were found to be 7.85×10^{-9} and 6.94×10^{-9} cm^2/s, respectively, while the drug diffusion coefficient for release at 37 °C was found to be 0.707×10^{-9} cm^2/s.

The effect of NIPAAm oligomers on the release behavior of P(HEMA-g-NIPAAm) gels was observed by comparing drug release profiles and drug diffusivities for plain PHEMA and P(HEMA-g-NIPAAm) gels. Drug release experiments were performed on PHEMA hydrogels using theophylline and inulin as model drugs. Drug release profiles for PHEMA gels loaded with theophylline at three temperatures (12, 25 and 37 °C) are shown in Fig. 5. The increase in release rate with temperature is theorized to be due to the increase in diffusion coefficient with temperature. For PHEMA gels loaded with inulin, the low solubilities of inulin in water made the release undetectable so results were not shown.

The grafted hydrogels displayed positive thermosensitivity as theophylline release from P(HEMA-g-NIPAAm) was significantly higher at 37 °C than 12 and 25 °C, where the grafts would be in their expanded state, blocking diffusion (Fig. 6). It was observed from the release profile that at all three temperatures, the gels continued to release the drug even after the 10 h release period. The release rate at 37 °C was faster because of the collapse of NIPAAm oligomers at temperatures higher than their LCST which increased the effective mesh size available for diffusion of theophylline. The release rates at 12 and 25 °C were slower owing to the presence of NIPAAm oligomers in the mesh space which were expanded at temperatures lower than their LCST. The difference in release rates at low temperature and high temperature was not very large because of the low graft density of 1 mol%. Further discussion on the change in diffusivity of the grafted (PHEMA-g-NIPAAm) network because of the presence of the grafts as opposed to the plain PHEMA network without the grafts is shown in later sections. Increasing the graft density would enhance the purpose of expanded oligomers at low temperatures which would further decrease or slow down the release at temperatures below the LCST of the grafted oligomers. This would show a bigger difference in release rates at temperatures below and above LCST of the oligomers.

The drug release profiles for the release of inulin from P(HEMA-g-NIPAAm) gels showed the expected positive thermoresponsive release rate (Fig. 7).

3.5. Drug diffusion coefficients

The cumulative release data were analyzed according to the early time approximation of the Fickian equation as given by (Brazel and Peppas, 2000):

$$\left(\frac{M_t}{M_\infty}\right) = 4\left(\frac{Dt}{\pi\delta^2}\right)^{1/2}, \qquad 0 \leq \left(\frac{M_t}{M_\infty}\right) \leq 0.6 \tag{4}$$

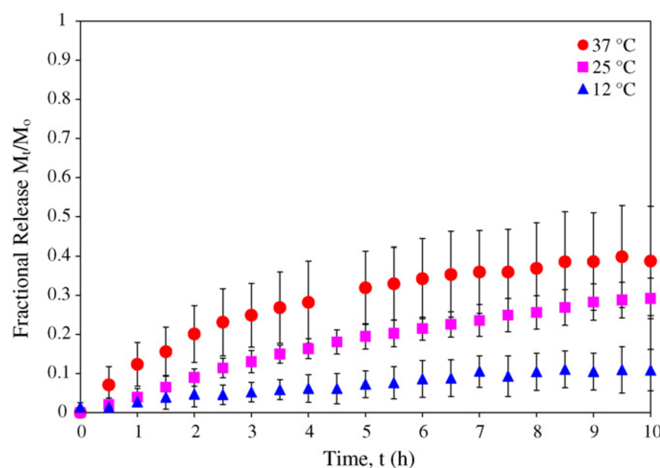

Fig. 7. Drug release profile for release of inulin from P(HEMA-g-NIPAAm) at three temperatures conducted in a Type II USP dissolution cell system. DI water was used as the release medium. Error bars indicate the standard deviation for three samples.

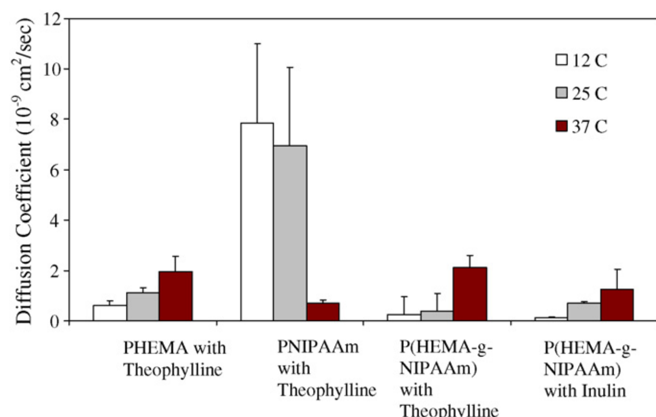

Fig. 8. Diffusion coefficients for drug release from PHEMA, PNIPAAm, and P(HEMA-g-NIPAAm) hydrogels at temperatures 12, 25 and 37 °C. Error bars indicate standard deviation for three samples. Where not shown, error bars are smaller than the data symbols.

Here M_t/M_∞ is the fractional drug released at time t. M_t is the mass of solute released at time t, M_∞ the total mass of solute that was released from the gel, and δ is the half thickness of the dry hydrogel sample disc. This analysis is valid for systems that exhibited Fickian behavior such as equilibrium swollen hydrogels containing dispersed drugs but it has been shown to give a good approximation even in swelling systems. In the drug release studies that were carried out, since the gels were still releasing the drug beyond the time period that the experiment was conducted in, the value of M_∞ is not known. So the amount of drug was normalized over the total amount of drug initially loaded instead of the total amount of drug that was released. So, M_∞ was substituted by M_o, the amount of drug that was loaded into the gels by equilibrium partitioning.

Using the above equations, diffusion coefficients for theophylline and inulin release from PHEMA, PNIPAAm and P(HEMA-g-NIPAAm) gels were calculated (Fig. 8). Drug diffusion coefficients for PHEMA gels loaded with theophylline increased with an increase in temperature. This increase in diffusion or release rate is dependent only on temperature and not on any thermal changes in the structure of PHEMA which is thermally nonresponsive as was observed from its swelling behavior. PNIPAAm gels allowed large drug diffusion coefficients at temperatures below the LCST (i.e., 12 and 25 °C) because of its negative thermosensitivity. The diffusion coefficient here is dependent on the thermal state of the PNIPAAm gel that is the increase in swelling ratio at 12 and 25 °C. The diffusion coefficient for theophylline release from PNIPAAm gel at 37 °C is 9.3% of the diffusion coefficient at 25 °C. At 37 °C, which is above the LCST of PNIPAAm, the gel shrinks thereby decreasing the release rate. However, the P(HEMA-g-NIPAAm) hydrogel shows small diffusion coefficients for both theophylline and inulin at low temperatures and a higher diffusion coefficient at 37 °C. The diffusion coefficients for theophylline release from PHEMA and P(HEMA-g-NIPAAm) at 37 °C are observed to be almost equal. This confirms that the oligomers which expanded at low temperatures did collapse at 37 °C and the presence of oligomers in the collapsed state did not hinder diffusion as the gel released the drug at the same rate as it would without the oligomers. A decrease in the values of $D_{\text{Theophylline}}$ from P(HEMA-g-NIPAAm) gels at 12 and 25 °C as compared to $D_{\text{Theophylline}}$ from PHEMA gels at the same temperature is attributed to the presence of PNIPAAm grafts which decrease the rate of diffusion by their thermosensitive behavior. Therefore, at 12 and 25 °C, the oligomers expanded and slowed down the release of theophylline. An increase in release rate of theophylline from P(HEMA-g-NIPAAm) owing to the collapse of PNIPAAm grafts at 37 °C resulted in a higher diffusion coefficient for P(HEMA-g-NIPAAm) gels at 37 °C. Diffusion coefficients for release of inulin through P(HEMA-g-NIPAAm) also showed the same trend but were small as compared to the Ds of theophylline for the same gels. This is due to a combination of the low aqueous solubility of inulin and its larger size (molwt 5200) compared to theophylline (molwt 180). Even with the oligomers collapsed at 37 °C, the mesh size was probably not large enough to allow faster diffusion of the inulin molecules (Fig. 8).

To determine if the grafts were effective at creating a positive thermal response, the ratios of diffusion coefficients for theophylline release at 25 and 37 °C were calculated. $(D^{37}_{\text{Theo,gel}}/D^{25}_{\text{Theo,gel}})$ for PHEMA was found to be 1.71, and $(D^{37}_{\text{Theo,gel}}/D^{25}_{\text{Theo,gel}})$ for P(HEMA-g-NIPAAm) was found to be 5.59. The increase in the diffusivity ratio for theophylline through the grafted system is due to changes in graft behavior with a low diffusivity through the P(HEMA-g-NIPAAm) hydrogels at low temperatures because of the expansion of the grafts. To further study the effect of oligomers incorporated into the PHEMA hydrogel on the diffusivity of theophylline through the grafted systems, the free solution diffusivities of theophylline in water at 25 and 37 °C were calculated by Stokes–Einstein equation:

$$D = \frac{kT}{6\pi\eta r} \tag{5}$$

Here, k is the Boltzmann constant, T the absolute temperature, η the viscosity of water and r is the hydrodynamic radius of theophylline molecule. $(D^{37}_{\text{Theo,free}}/D^{25}_{\text{Theo,free}})$ calculated from Eq. (5) was found to be 1.34. The increased diffusivity due to temperature increase was responsible for a significant portion of the increase observed in PHEMA gels, while graft contraction must account for the larger diffusivity increase in P(HEMA-g-NIPAAm) gels.

4. Conclusions

While our goal of creating a thermally triggered delivery system will require a much greater change in diffusivity across the LCST, the grafted hydrogel system shows the feasibility of the system in achieving a positive thermal response. Drug release experiments on PNIPAAm gels loaded with theophylline clearly showed the negative thermal response of PNIPAAm with a faster release at low temperature when it is completely swollen and a slow release rate at higher temperatures when it is collapsed. Based on this behavior of PNIPAAm, a drug delivery system

with PNIPAAm oligomers grafted onto PHEMA was designed and tested. The release profile for the release of model drugs from the newly grafted hydrogel system, P(HEMA-g-NIPAAm), showed the expected positive thermoresponsive release trend of higher release rate at 37 °C and significantly lower release rate at 12 °C. This result is encouraging for further work to develop sharp thermosensitive drug carriers that can be triggered to release their payload by a heating event.

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